Aus dem Zentrum für Operative Medizin der Universität zu Köln
Klinik und Poliklinik für Allgemein-, Viszeral- und Tumorchirurgie und
Transplantationschirurgie
Direktorin: Universitätsprofessorin Dr. med. C. Bruns

Emerging therapy options for gastric adenocarcinoma - a comprehensive review and analysis of clinical trials

Inaugural-Dissertation zur Erlangung der Doktorwürde
der Medizinischen Fakultät
der Universität zu Köln

vorgelegt von
Milan Janis Michael Hartmann
aus Würzburg, Deutschland

promoviert am 27. April 2026

Gedruckt mit Genehmigung der Medizinischen Fakultät der
Universität zu Köln sowie das Jahr der Erstellung (2026)

Dekanin/Dekan: Universitätsprofessor Dr. med. G. R. Fink

1. Gutachter: Professor Dr. med. H. Alakus
2. Gutachter: Privatdozent Dr. med. A. Calaminus

Ich erkläre hiermit, dass ich die vorliegende Dissertationsschrift ohne unzulässige Hilfe Dritter und ohne Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe; die aus fremden Quellen direkt oder indirekt übernommenen Gedanken sind als solche kenntlich gemacht.

Bei der Auswahl und Auswertung des Materials sowie bei der Herstellung des Manuskriptes habe ich keine Unterstützungsleistungen.

Weitere Personen waren an der Erstellung der vorliegenden Arbeit nicht beteiligt. Insbesondere habe ich nicht die Hilfe einer Promotionsberaterin/eines Promotionsberaters in Anspruch genommen. Dritte haben von mir weder unmittelbar noch mittelbar geldwerte Leistungen für Arbeiten erhalten, die im Zusammenhang mit dem Inhalt der vorgelegten Dissertationsschrift stehen.

Die Dissertationsschrift wurde von mir bisher weder im Inland noch im Ausland in gleicher oder ähnlicher Form einer anderen Prüfungsbehörde vorgelegt.

Ich war alleinig für die Erstellung, Bearbeitung und Auswertung der Datensätze verantwortlich und habe alle Arbeit selbst geleistet.

Erklärung zur guten wissenschaftlichen Praxis:

Ich erkläre hiermit, dass ich die Ordnung zur Sicherung guter wissenschaftlicher Praxis und zum Umgang mit wissenschaftlichem Fehlverhalten (Amtliche Mitteilung der Universität zu Köln AM 132/2020) der Universität zu Köln gelesen habe und verpflichte mich hiermit, die dort genannten Vorgaben bei allen wissenschaftlichen Tätigkeiten zu beachten und umzusetzen.

Köln, den 11. Juli 2025

Unterschrift: .....

Danksagung

An dieser Stelle möchte ich allen beteiligten Personen meinen großen Dank aussprechen, die mich bei der Anfertigung und der Bearbeitung meiner Dissertation unterstützt haben.
Mein besonderer Dank gilt Prof. Dr. med. Hakan Alakus für die enorme Unterstützung und Betreuung bei der Durchführung und Umsetzung der gesamten Arbeit, sowie die Möglichkeit Teile dieser Arbeit zu veröffentlichen. Seine Geduld und Wertschätzung möchte ich dabei besonders hervorheben. Zudem möchte ich mich bei Prof. Dr. med. Costanza Chiapponi bedanken, die mich im Rahmen meines Studiums und Publikation mit einbezogen hat und mit Anregungen und Worten begleitet hat.
Des weiteren, möchte ich zudem Univ.-Prof. Dr. med. Christiane Bruns, der Direktorin der Klinik und Poliklinik für Allgemein-, Viszeral-, Tumor- und Transplantationschirurgie der Universität zu Köln meinen Dank äußern.
Für den Zugang zu Adis Insight danke ich Daniela Ranzani.
Außerdem möchte ich meiner Frau, meinen Kindern, sowie meinen Eltern für ihre Geduld und Ermutigungen während der Arbeit an dieser Doktorarbeit von ganzen Herzen danken.

Table of contents

Table of abbreviations

5-FU *5-fluorouracil*

ADC ..... *antibody drug conjugate*

AF-HPA ..... *12 auristatin F-hydroxypropylamide*

AGC ..... *Advanced gastric cancer*

AJCC ..... *American Joint committee on Cancer*

Akt ..... *protein kinase B*

AML ..... *acute myeloid leukemia*

APC ..... *Adenomatous polyposis coli*

ARHGAP ..... *Rho GTPase Activating Protein 1*

ATR ..... *ataxia telangiectasia and Rad3-related*

AXL ..... *gene for tyrosine-protein kinase receptor UFO*

Bcl-2 ..... *B-cell lymphoma 2*

BCL2 ..... *B-cell leukemia/lymphoma 2 protein*

BER ..... *base excision repair*

Ca^{2+} ..... *calcium ion*

cAMP ..... *Cyclic adenosine monophosphate*

CapeOx ..... *oxaliplatin and cabecitabine*

CAR T ..... *chimeric antigen receptor T-cell*

CCND2 ..... *G1/S-specific cyclin-D2 is a protein that in humans is encoded by the CCND2 gene*

CD4 ..... *cyclin dependent kinases 4*

CDH1 ..... *Cadherin 1, Cadherin-1*

CDK ..... *cyclin-dependent kinase*

CFDA ..... *China National Food and Drug administration*

CGA ..... *cardia gastric adenocarcinoma*

CI.. ..... *confidence intervall*

CIN ..... *chromosomal unstable*

CK2 ..... *casein kinase II*

CLDN18 ..... *Claudin 18*

CPS ..... *combined positive score, combined positive score*

CSNK2A1 ..... *casein kinase II*

CT. ..... *computed tomography*

DDR2 ..... *discoidin domain receptor 2*

DKK1 ..... *dickkopf-1*

DM1 ..... microtubule-depolymerizing maytansinoid derivative

DNA ..... *Deoxyribonucleic acid*

DR5 ..... *death receptor 5*

EBV ..... *Epstein-Barr Virus*

EBV+ ..... *Epstein-Barr virus positive*

ECM.....*extracellular matrix*

ECX.....*epirubicin, cisplatin and capecitabine*

EFC.....*epirubicin, cisplatin and 5-fluorouracil*

EGC.....*Early gastric cancer*

EGFR.....*Epidermal Growth Factor Receptor*, *epidermal growth factor receptor*

EMR.....*endoscopic mucosal resection*

EPHB1.....*Eph receptor B1*

ER.....*Estrogen receptors*

ERBB2.....*Erb-B2 Receptor Tyrosine Kinase 2*

ERBB3.....*Erb-B2 Receptor Tyrosine Kinase 3*

ESCC.....esophageal squamous cell carcinoma

ESD.....*endoscopic submucosal dissection*, *endoscopic submucosal dissection*

ESMO.....*European Society for Medical Oncology*

EUS.....*endoscopic ultrasound*

FAK.....*focal adhesion kinase*

FAP.....*familial adenomatous polyposis*

FDA.....*the US Food and Drug Administration*, *U.S. Food and Drugs association*

FGFR3.....*fibroblast growth factor receptor 3*

FLOT.....*fluorouracil, leucovorin, oxaliplatin and docetaxel*

FLT1.....*vascular endothelial growth factor 1*

FLT3.....*FMS-like tyrosine kinase 3*

FLT4.....*vascular endothelial growth factor 3*

FOLFOX.....*oxaliplatin, leucovorin and fluorouracil*

FP.....*Cisplatin and 5-fluorouracil*

FZD.....*Frizzled-1*

GAPPS.....*proximal polyposis of the stomach*

GC.....*Gastric cancer*

GEJ.....*gastroesophageal junction*

GERD.....*Gastroesophageal reflux disease*

GIST.....*gastrointestinal stromal tumors*, *gastro-intestinal tumors*

Gy.....*Gray*

HDGC.....*hereditary diffuse gastric cancer*

HER-2.....*human epidermal growth factor receptor 2*

HGFR.....*hepatocyte growth factor receptor*

HIF-1.....*Hypoxia-inducible factor 1*

HR.....*hazard ratio*

IDO1.....*indoleamine 2,3-dioxygenase-1*

IgM.....*immunoglobulin M*

IL.....*Interleukin*

IL-6.....*Interleukin 6*

ILT2.....*immunoglobulin like transcript 2*

ILT4.....*immunoglobulin like transcript 4*

JAK2.....*Janus kinase 2*

Jak-STAT ..... • *Janus kinase-signal transducer and activator of transcription*

KDR ..... *vascular endothelial growth factor 2*

KEGG ..... *kyoto encyclopedia of genes and genomes*

KIT ..... *gene for mast/stem cell growth factor receptor*

LAG-3 ..... *lymphocyte-activation gene*

mAb ..... *monoclonal antibody*

MAPK ..... *mitogen-activated protein kinases*

MDM2 ..... *murine double minute 2*

MERTK ..... *the receptor tyrosine kinase MER*

MET ..... *gene for hepatocyte growth factor receptor*

MLH1 ..... *mutL homolog 1*

MMAE ..... *Monomethyl auristatin E*

MMP9 ..... *matrix metalloproteinase 9*

MSD ..... *myelodysplastic syndromes*

MSI ..... *microsatellite instable*

mTOR ..... *mechanistic target of rapamycin, mammalian target of rapamycin*

MYCN ..... *N-myc proto-oncogene protein*

NCT ..... *Nationa Clinic trial Identifier*

NRG1 ..... *neregulin-1*

NSCLC ..... *non-small cell lung cancer*

NTRK1 ..... *gene for tropomyosin receptor kinase A*

OR. ..... *odds ratio, overall response*

OS ..... *Overall survival*

PARP ..... *Poly(ADP-ribose) polymerase*

PAX ..... *human paired box*

PDCD1LG2 ..... *programmed cell death 1 ligand 2*

PDGFR ..... *platelet-derived growth factor receptor*

PD-L1 ..... *programmed cell death 1 ligand 1, programmed cell death 1 ligand 1*

PD-L2 ..... *programmed cell death 1 ligand 2*

PET ..... *positron emission tomography*

PFS ..... *progression free survival*

PI3K ..... *phosphatidylinositol 3-kinase*

PI3Kβ ..... *beta isoform of phosphoinositide-3 kinase*

PI3KCB ..... *beta isoform of phosphoinositide-3 kinase*

PIK3CA ..... *Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha*

PKA ..... *protein kinase A*

PKB ..... *protein kinase B*

PORCN ..... *porcupine*

PPG ..... *pylorus-preserving gastrectomy*

PPI ..... *proton pump inhibitors*

PRL3 ..... *phosphatase of regenerating liver 3*

PTP4A3 ..... *gene for phosphatase of regenerating liver 3*

RAS ..... *Rat sarcoma virus*

RET ..... *rearranged during transfection*

RHOA ..... *Ras Homolog Family Member A*

RR ..... *relative risk, Overall relative risk*

RTK ..... *Receptor tyrosine kinases*

S-1 ..... *Tegafur-gimeracil-oteracil potassium combination*

SCFR ..... *mast/stem cell growth factor receptor*

SERD ..... *selective estrogen receptor degraders*

SERM ..... *selective estrogen receptor modulators*

SGMIB ..... *N-succinimidyl 4-guanidino-methyl-3-iodobenzoate*

SLC6A8 ..... *solute carrier family 6 member 8*

SLC7A11 ..... *solute carrier family 7 member 11*

SOX ..... *oxaliplatin and Tegafur-gimeracil-oteracil potassium combination (S-1)*

STAT3) ..... *signal transducer and activator of transcription 3*

TCGA ..... *The Cancer Genome Atlas, The Cancer Genome Atlas*

TGF ..... *transforming growth factor*

TGFBR1 ..... *transforming growth factor (TGF)-beta receptor type 1*

TP53 ..... *Tumor protein 53, tumor protein p53 gene*

TPS ..... *tumor proportional score*

TRK ..... *tropomyosin-related kinases*

TrkA ..... *tropomyosin receptor kinase A*

TROP2 ..... *trophoblast antigen 2*

TRPC6 ..... *transient receptor potential channel 6*

TRPM8 ..... *transient receptor potential melastatin family member 8*

UICC ..... *Union for International Cancer Control*

VEGF ..... *vascular endothelial growth factor*

VEGFR ..... *vascular endothelial growth factor receptor 2*

WHO ..... *World Health Organization, World Health Organization*

XELOX ..... *oxaliplatin and capecitabine*

XIAP ..... *X-linked inhibitor of apoptosis protein*

1 Summary

Gastric adenocarcinoma continues to be a significant global health burden and ranking among the top five leading causes of cancer-related mortality. Although there have been advancements in surgical and chemotherapeutic strategies, the prognosis for advanced and metastatic stages is still poor, stressing the urgency for more effective and personalized treatment options.

This thesis explored the landscape of targeted therapies that are currently under investigation for the treatment of gastric adenocarcinoma, with the focus on active and completed clinical trials to comprehend new arising options for treatment. We utilized databases such as ClinicalTrials.gov, DrugBank, KEGG, and PubMed, and provided a comprehensive analysis to identify the range of molecular targets, therapeutic classes, and biological pathways involved. The study reviewed the already approved therapies and distinguished 2433 clinical trials investigating 905 investigational agents targeting 320 distinct molecular pathways or gene products. Among the most promising targets under investigation are CLDN18.2, FGFR2b, MET, and immune checkpoint combinations, alongside antibody-drug conjugates and bispecific antibodies. The thesis further integrated genomic and signaling pathway analysis using data from KEGG and TCGA, highlighting frequently altered pathways such as PI3K/Akt, RTK-RAS, p53, TGF-β, and Wnt/β-catenin. A network analysis of target gene interactions underscores the necessity of multi-targeted and biomarker-enriched strategies as well as further research to deepen the understanding molecular composition of gastric cancer.

While overall there are several promising trials and agents, the current therapeutic pipeline faces various challenges, especially limited biomarker availability, variability in treatment response across patient populations, and a general need for more extensive inclusion criteria in clinical trials. This means we need to further deepen our understanding of molecular profiling, adaptive trial designs, and personalize treatment approaches.

In conclusion, the field of targeted therapy for gastric cancer is still rapidly evolving. With continued innovation and a shift toward biomarker-guided treatment, there is hope to significantly improve patient outcomes and transition from generalized treatment paradigms to precision oncology as in most of the other carcinoma. This work provides a structured overview of ongoing developments and contributes to the growing body of knowledge essential for advancing gastric cancer therapy.

Deutsche Fassung: „Neue Therapieoptionen für das Magenadenokarzinom – eine umfassende Übersicht und Analyse klinischer Studien“

Das Magenkarzinom stellt weltweit immer noch eine der häufigsten Ursachen krebsbedingter Todesfälle dar. Die Mehrheit der Patient*innen wird erst in einem fortgeschrittenen, inoperablen Stadium diagnostiziert, was die Notwendigkeit effektiver therapeutischer Alternativen unterstreicht. Während konventionelle Chemotherapie nur begrenzte Überlebensvorteile bieten, haben Fortschritte in der molekularen Onkologie zur Entwicklung zielgerichteter Therapien geführt, die personalisierte und präzisere Behandlungsansätze ermöglichen. Diese Arbeit bietet eine umfassende Analyse der derzeit zugelassenen zielgerichteten Therapien sowie vielversprechender neuer Therapieansätze beim Magenkarzinom.

Untersucht wurden neben den bereits zugelassen Therapien 2433 klinische Studien ausgewertet, in denen 905 nicht zugelassene Substanzen identifiziert wurden, die auf insgesamt 320 verschiedene molekulare Zielstrukturen abzielen. Besonders vielversprechende Ziele sind CLDN18.2, FGFR2b, MET sowie neue Kombinationen von Immuncheckpoint-Inhibitoren und Antikörper-Wirkstoff-Konjugaten (ADCs).

Ein weiterer Fokus dieser Arbeit liegt auf der Analyse wichtiger Signalwege, basierend auf Daten aus den KEGG- und TCGA-Datenbanken. Hierbei wurden besonders häufig veränderte Signaltransduktionswege wie PI3K/Akt, RTK-RAS, p53, TGF-β und Wnt/β-Catenin identifiziert. Eine Netzwerk-Analyse der Zielgene zeigt zentrale molekulare Schnittstellen auf, die das therapeutische Potenzial kombinierter Therapieansätze unterstreichen und die Notwendigkeit biomarkerbasierter Therapiestrategien verdeutlichen.

Darüber hinaus widmet sich diese Arbeit zukunftsweisenden Ansätzen wie der personalisierten Immuntherapie, einschließlich CAR-T-Zelltherapien und neoantigenbasierten Krebsimpfstoffen. Trotz vielversprechender präklinischer und erster klinischer Daten stellen solide Tumoren wie das Magenkarzinom aufgrund von Antigenheterogenität, immunsuppressivem Tumormikromilieu und physikalischen Barrieren eine besondere Herausforderung dar.

Insgesamt liefert diese Arbeit eine strukturierte Übersicht über den aktuellen Stand und die zukünftige Entwicklung zielgerichteter Therapien beim Magenkarzinom. Sie identifiziert außerdem vielversprechende neue Therapieziele, ordnet sie in ihren molekularbiologischen Kontext ein und skizziert künftige Perspektiven der Präzisionsonkologie. Die Kombination aus molekularer Diagnostik, innovativen Wirkstoffen und datengetriebener Entscheidungsunterstützung verspricht, die Behandlung dieser komplexen Tumorerkrankung nachhaltig zu verbessern.

2 Introduction

2.1 Gastric Cancer

2.1.1 Epidemiology

Although the incidence and mortality rates are decreasing steadily over the past decades, gastric cancer (GC) is still one of the most frequent causes of death worldwide(Sung et al., 2021; M. C. S. Wong et al., 2021). Every year over one million cases are diagnosed and about 769 000 deaths are tributed to GC(Sung et al., 2021). GC is the fifth most frequently diagnosed cancer with 5.6% of the cancer cases worldwide and responsible for about 7.7% of all cancer deaths, ranked fourth in mortality(M. C. S. Wong et al., 2021). In general GC is diagnosed about twice as much in males (global incidence: 719,523; incidence: 7.1%; mortality 9.1%) as in females (369,580; 4.0%; 6.0%) (Sung et al., 2021). There are regional differences worldwide too, with about 75% of the new cases localized in Asia, 13.5% in Europe, 6.2% in Latin America, 3% in Africa and 2.7% in Northern America(Ferlay et al., 2018). More detailed differences in distribution are shown in Figure 1 with Eastern Asia, especially Japan for males and Mongolia for women, and Eastern Europe as the regions with the highest age-standardized incidence rate per 100,000(Ferlay et al., 2018; Sung et al., 2021). There is also a higher frequency of gastric cancer in developed countries than in industrial countries where numbers of GC have been steadily decreasing(Balakrishnan, George, Sharma, & Graham, 2017; Sung et al., 2021). Countries with gastric cancer as the leading cause of the death are for example, Afghanistan, Iran, and Turkmenistan(Sung et al., 2021).

In Germany stomach cancer showed lower incidence (3.5% for male patients; 2.4% for females patients) and mortality rates (4.2%; 3.5%) in 2017/2018(RKI, 2021). The 5-(10) year survival rate is still lower than most other cancer entities with about 34% (30%) for male patients and about 37% (33%) for female patients(RKI, 2021).

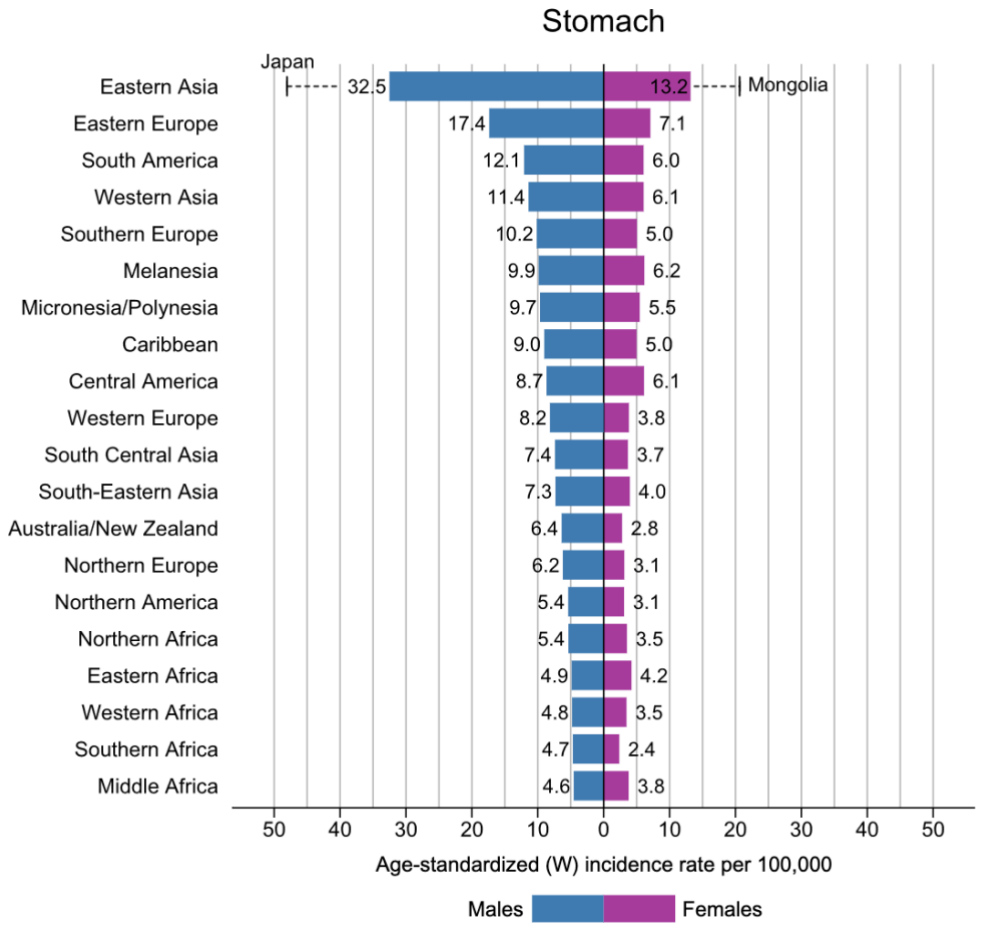


Figure 1 Region-Specific Incidence Age-Standardized Rates by Sex for Stomach Cancer in 2020. Rates are shown in descending order of the world (W) age-standardized rate among men, and the highest national rates among men and women are superimposed. Source: GLOBOCAN,(Sung et al., 2021)

2.1.2 Etiology

GC is a diverse malignancy with numerous linked to a wide spectrum of environmental, lifestyle and genetic factors, of which not all have been fully explored(Cheng, Lin, & Tu, 2016). Due to developments in preventions, screening programs and improvements in the food processing industry incidence and mortality have been continuously decreasing the last fifty years, but there are new trends emerging that must be observed carefully(Balakrishnan et al., 2017). In the following the main risk factors and their pathogenesis are discussed.

2.1.3 Pathogeneses and risk factors

There are several risk factors increasing the chance of developing a stomach cancer. Here are some of the most common risk factors and their pathogeneses, of which H. pylori, genetics, diet and lifestyle are strongly associated with GC(Karimi, Islami, Anandasabapathy, Freedman, & Kamangar, 2014):

i. Helicobacter pylori

Chronic infection with *H. pylori* can cause the mucosa of the stomach to gradually develop from a atrophic gastritis to intestinal metaplasia(Elizabeth C. Smyth, Nilsson, Grabsch, van

Grieken, & Lordick, 2020). This can be caused by the direct epigenetic impact of *H. pylori* on the gastric epithelial cells or the indirect inflammatory reaction of bacteria on the mucosa(Ishaq & Nunn, 2015). A typical gastric cancer type caused by *H. pylori* infection is the non-cardia subtype(Mukaisho, Nakayama, Hagiwara, Hattori, & Sugihara, 2015).

In 1994 *H. pylori* was declared a class I carcinogen for gastric cancer by the World Health Organization (WHO), when studies showed strong evidence for increased incidence of gastric adenocarcinoma in patients with a *H. pylori* infection(Nomura et al., 1991; Parsonnet et al., 1991). Since then the steady decline in incidence and mortality of GC is not mostly attributed to new therapy options or the invention of a cure, but mainly to prevention like a decreased prevalence of *H. pylori* and advances in the food industry(Howson, Tomohiko, & Wynder, 1986). *H. pylori* is still the main risk factor for gastric cancer and causes up to 80% of gastric ulcer(Ahmed, 2005), but first preventive screenings of *H. pylori* have showed effectiveness on gastric cancer incidence and mortality in regions with high frequencies like Japan(Hamashima et al., 2013) and Korea(H. Kim et al., 2018). Nowadays there are different trends and opinions about the role that *H. pylori* still plays. There is an appeal to substantially eradicate H. pylori to gain control over high incidence regions like Latin America and East Asia(Balakrishnan et al., 2017), but there is also a plea that H. pylori actually has a symbiotic relationship with humans that causes a lot of advantages like reducing the risk for esophageal inflammation, cardia gastric cancer, asthma or obesity(Mukaisho et al., 2015; Rawla & Barsouk, 2018). There are findings that there is an increase in the cardia subtype gastric cancer as well as a growing incidence of noncardiac cancers of the stomach in younger adults, which could originate from an increased application of antibiotics and acid suppressants(Anderson et al., 2018; Camargo et al., 2011). Additionally, is GC found more regularly in ethnic and racial minorities, as well as in population with low socioeconomic status and treatment of an *H. pylori* infection only decrease the risks for cancer of the stomach if the infection was totally eradicated after treatment(Kumar, Metz, Ellenberg, Kaplan, & Goldberg, 2020).

ii. Genetics

Hereditary GC is not very common and is not widely reported apart from syndromes like the hereditary diffuse gastric cancer (HDGC), familial adenomatous polyposis (FAP), and proximal polyposis of the stomach (GAPPS)(Karimi et al., 2014). Only 1 – 3% of cases have been linked to genetic variants. In HDGC a mutation in the CDH1 gene as well as the loss of one copy of the same gene causes this syndrome(Rawla & Barsouk, 2018). FAP is known to be a result of germline mutation in the APC gene, which can lead to adenomatous polyps, which then can cause GC(Boland & Yurgelun, 2017; Rawla & Barsouk, 2018). GAPPS has been shown to be a variant of FAP and be able to induce polyposis with an increased risk to develop into a cancer of the stomach(J. Li et al., 2016). On the other hand there are single/nucleotide polymorphisms that are affiliated to GC in several studies(Abnet et al., 2010; Sakamoto et al., 2008; Y. Shi et

al., 2011; L.-D. Wang et al., 2010), like Interleukin (IL) polymorphisms(Kamangar, Cheng, Abnet, & Rabkin, 2006). Especially IL-17 and IL10, as well as IL-1B polymorphisms are associated with higher risk for GC(Boland & Yurgelun, 2017). In total the risk to obtain GC is 2 to 3 times higher if you have one first-degree relative diagnosed with GC and about ten times higher if you have more than one first-degree relative with GC. It is not totally settled how much influence is tributed to a mutual lifestyle and/or genetics(RKI, 2021; Yaghoobi, McNabb-Baltar, Bijarchi, & Hunt, 2017).

iii. Gastroesophageal reflux and gastric atrophy

Gastroesophageal reflux disease (GERD) is strongly associated with developing an esophageal adenocarcinoma and to a lower degree with cardia gastric cancer(Ye, Chow, Lagergren, Yin, & Nyrén, 2001). Additionally gastric atrophy is linked strongly to non-cardia gastric cancer(Derakhshan et al., 2008). Looking at the trends in GC, incidence rates originated by GERD have been continually increasing in contrast to incidence rates for GC caused by *H. pylori* (Abrams, Gonsalves, & Neugut, 2013). The pathogenesis for esophageal adenocarcinoma and cardia GC is thought to be originating from a related source as the incidence trends are very homogenous(Demicco et al., 2011). In general is mucosa tissue at the cardia and the esophageal junction put under stress through constant penetration with acids, which can lead to dysplastic intestinal metaplasia and finally to GC or esophageal (junction) adenocarcinoma(Demicco et al., 2011). So far GERD is managed to provide symptomatic relief and investigate for adjustments in lifestyle before prescribing pharmaceuticals like proton pump inhibitors (PPI) or even surgery(Katzka & Kahrilas, 2020). Overall GERD is increasing risk for cardia gastric adenocarcinoma (CGA) by two to four times(Abdi, Latifi-Navid, Zahri, Yazdanbod, & Pourfarzi, 2019).

iv. Smoking and alcohol

Lifestyle factors also contribute to an increased risk for GC. In particular, smoking and alcohol consumption have been associated with an increased risk. A meta-analysis including forty-two studies even categorized smoking as the most significant behavioral risk factor for gastric cancer(Ladeiras-Lopes et al., 2008). The relative risk (RR) in males was 1.62 (95% CI 1.50 - 1.75; I^2: 46.0%; 18 studies) and in females 1.20 (95% CI: 1.01 - 1.43; I^2= 49.8%; nine studies) with an increasing risk the higher the consumption was. Alcohol on the other hand is still being investigated as one meta-analyses found an increased risk for drinking alcohol regularly by 39%(Ma, Baloch, He, & Xia, 2017) and another meta-analysis discovered an enlarged risk for only heavy drinking ($\geq$ 4 drinks a day) by about 20%, but no significant difference in regular alcohol drinkers(Tramacere et al., 2012). It is known though that there is an association between alcohol and an erosion of mucosa, which can lead to gastritis and is a acknowledged progenitor for GC(G. Li et al., 2018; Ma et al., 2017).

v. Diet and obesity

Another huge lifestyle component on increasing the risk for GC is the diet and/ or the obesity. There are a lot of meta-analyses on dietary influence towards GC with findings for increased risk for salt (OR: 3.78; 95% CI: 1.74-5.44; and OR: 1.34; 95% CI: 0.88-2.03))(Poorolajal, Moradi, Mohammadi, Cheraghi, & Gohari-Ensaf, 2020) and meat (OR: 1.30: 95% CI:1.09-1.55)(Ferro, Rosato, et al., 2020) in general, and especially red and processed meat. Decreasing dietary factors are known to be consumption of fruits ≥3 times per week (OR: 0.48; 95% CI: 0.37-0.63)(Poorolajal et al., 2020), higher intake of fruits (OR: 0.76, 95% CI: 0.64-0.90)(Ferro, Costa, et al., 2020), noncitric fruits (OR: 0.86, 95% CI: 0.73-1.02)(Ferro, Costa, et al., 2020), citrus fruits (OR: 0.81; 95% CI: 0.74-0.89)(Bertuccio et al., 2019), vegetables (OR: 0.68, 95% CI: 0.56-0.84)(Ferro, Costa, et al., 2020), and fruits and vegetables (OR: 0.61, 95% CI: 0.49-0.75)(Ferro, Costa, et al., 2020); Obesity in general shows a higher risk for cancer in many different types of cancer(Renehan, Tyson, Egger, Heller, & Zwahlen, 2008) and has also shown it for gastric cancer (OR: 1.22; 95% CI=1.06-1.41)(Yang et al., 2009). Generally, dietary modifications should be adjusted for subgroups and populations to achieve better results as there are differences for examples in adaption to salt intake(Yang Guo et al., 2020).

vi. Epstein-Barr Virus

The Epstein-Barr Virus (EBV) has displayed major influences on increased risk for GC. About 5-10% of gastric cancers in Germany(RKI, 2021) and 2-16% in other populations(Boysen et al., 2009; Burgess et al., 2002; Murphy, Pfeiffer, Camargo, & Rabkin, 2009; Shibata & Weiss, 1992) are tributed to EBV. EBV-positive cases normally originated from one cell and nucleic acid sequences of the same EBV virus can be found in all tumor cells(Murphy et al., 2009). Although prognosis varies by stage, EBV-positive GCs generally have a favorable prognosis and may be associated with improved responsiveness to immunotherapy(Sun et al., 2020).

vii. Others

There are other factors discussed in literature as well. Pernicious anemia for example has shown an almost seven times bigger risk for GC than in the normal population. But the connection is still not resolved as investigations have shown that gastritis can cause a vitamin B12 deficiency which can lead to a pernicious anemia(Vannella, Lahner, Osborn, & Annibale, 2013). Another risk factor is a previous gastric surgery and could lead to a so-called gastric stump cancer. The overall relative risk (RR) is increased by 1.66 (95% CI: 1.54-1.79) in a meta-analysis with higher risk for a Billroth II (RR:. 1.60; CI: 1.15-2.18) gastrectomy than for Billroth I Gastrectomy (RR: 1.20; 95 CI: 1.01-1.42)(Tersmette et al., 1990). Other risk factors for GC shown in literature are radiation(environmental radiation(Henderson et al., 2012; Preston et al., 2007) as well as therapeutic radiation(Hauptmann et al., 2015; Morton et al., 2013)), exposure to mineral dusts such as asbestos(Fortunato & Rushton, 2015), talc(Chang, Tu, Chen, & Yang, 2020) or crystalline silica(W. Lee et al., 2016) and socioeconomic status(Cattelan et al., 2021; Lyons et al., 2019), which is closely linked to lifestyle factors.

2.1.4 Pathology

GC is a heterogeneous malignancy related to various environmental, genetic and habitual predispositions(Cheng et al., 2016). The main type of gastric cancer is an adenocarcinoma that can be divided into cardia and non-cardia adenocarcinomas(Rawla & Barsouk, 2018). This division is based on their location in the stomach with the cardia being the entry into the stomach. The majority of GC (about 95%) of is an adenocarcinoma. Other types of cancer of the stomach are for examples gastrointestinal stromal tumors (GIST), neuroendocrine tumors and primary gastric lymphomas.

2.1.5 Classification of gastric cancer

There are various classifications based on histology, pathology, anatomic location, surgery options or molecular pathology and most important ones are introduced in the following.

i. Early gastric cancer

Early gastric cancer (EGC) was first described in Japan in 1971 and was defined as “carcinoma limited to the mucosa and/or submucosa regardless of the lymph node status”(Murakami, 1971). Most of the carcinomas are limited to a size of 2 to 5 cm and mostly located at the lesser curvature(Hu et al., 2012). There are four general categories for EGC. Type I stands for carcinomas with protruding growth, Type II for external growth, Type II for excavating expansion and Type IV for penetrating growth with lateral proliferation. Type II can be further divided into IIa as elevated, IIb as flat and IIc as depressed as suggested by the Japanese Endoscopic Society(Murakami, 1971).

If there are only lesions in the mucosa there is a 5-year survival rate of up to 100% and if the submucosa is impacted the rates drop to about 90%(Inoue et al., 1991). In general, an early stage of GC is meant to be categorized in which the malignancy hasn’t been able to spread, but its disregard to the lymph node status has set off debates to a renewal of the definition(Saragoni, 2015). ECG is still considered an early stage of the cancer with an overall good prognosis. There is a though a wide spectrum of EGC from non-threatening ECG with a 5-year survival rate of 98-100% and ECG with lymph node metastasis and a 5-year survival rate of about 70%(Saragoni, 2015). The incidence of ECG is much higher in Asian countries as there are screening programs in effect and lower in other countries with no screening programs(Zong, Abe, Seto, & Ji, 2016). Overall, the 5-year survival rate is 90%(Everett & Axon, 1997).

ii. Advanced gastric cancer

Advanced gastric cancer (AGC) however is defined by the infiltration into the muscularis propria or further and entails a worse 5-year survival rate than EGC at about 60%(K. Yoshikawa & Maruyama, 1985). AGC is also more common in the lower part of the stomach and the lesser curvature. The overall manifestation can be exophytic, ulcerated, infiltrative or

a combination of these. There is also a classification for the AGC according to Borrmann by its macroscopic appearance.

The Borrmann classification divides advanced gastric cancer into four types: type I is characterized as a polypoid growth, type II as a fungating proliferation, type III as an ulcerating expansion and type IV as a diffusely infiltrating growth(Borrmann, 1926). Type IV is considered a prognostic factor for advanced gastric cancer and has the lowest overall 5-year survival rate and is thereby linked to the worst outcome(An et al., 2008). Type I normally doesn't penetrate the serosa and thereby has a better prognosis, and type II and III are hard to differentiate when adjacent mucosa is inflamed and irritated(C. Yan et al., 2016). Different types of the Borrmann classification are therefore associated with different outcomes and different therapy guidelines. The main type with highest incidence is Borrmann type III with approximately 70% of the cases, followed by about 15% for type IV, 13% for type II and only 3% for type I(S. Wang et al., 2021). It is important to distinguish between EGC and AGC before resecting the malignancy because it has influence on the treatment concept and for example if neoadjuvant therapy is necessary to achieve better disease free and overall survival rates(David Cunningham et al., 2006). If the carcinoma has infiltrated lymph nodes as well, the overall 5-year survival rate drops to 20 to 30%(Siewert et al., 1993). Therefore, a detailed assessment of the GC is necessary which entails according to guidelines not only the outer appearance but also an endoscopic ultrasonography and computer tomography as well as a histological classification(Hwang et al., 2010).

iii. Histopathological Classification

A histopathological classification is very important because it provides a better understanding of the origin and the approach of the malignancy and is the gold standard nowadays. There are different classifications based on the histopathology of GC and the most important are shown here.

a. Lauren Classification

The Lauren classification has been the foundation for classifications in GC since 1965. There are two main types of adenocarcinomas, an intestinal type, and a diffuse type. The intestinal type is a well-differentiated type of cancer with a better prognosis and a higher incidence in males(AACR, 2018), while diffuse adenocarcinomas of the stomach are harder to treat and are less common in general, but occur more often in younger adults and women(Chon et al., 2017). There is also indeterminate type as a more uncommon variant, which is found in about 15% of the cases while the intestinal type occurs in about 54% and the diffuse type in about 32%(Polkowski et al., 1999).

The intestinal adenocarcinoma is characterized as a formation of visible glands with generally cohesive cells. It has been shown that intestinal adenocarcinomas are more frequently originated from intestinal malignancies and are more frequently linked to a *h. pylori* infection.

Diffuse adenocarcinomas on the other hand have more loosely arranged tumor cells that derived from the gastric mucosa and don't usually show gland or tubular formations(Machlowska, Baj, Sitarz, Maciejewski, & Sitarz, 2020). There has been an ongoing debate of whether the Lauren classification is still a contemporary approach as it only includes adenocarcinomas and doesn't necessarily provided a prognostic value or clear therapeutic guidelines without further categorization(Hu et al., 2012).

b. WHO Classification

The Classification by the World Health Organization (WHO) was introduced in 2010(Bosman, Carneiro, Hruban, & Theise, 2010), updated last in 2019(Nagtegaal et al., 2020) and is the most in detail categorization of GC. It identifies four main patterns of GC: papillary, mucinous, tubular and poorly cohesive. There is also an addition of more uncommon types that can't be categorized into any of those types is not limited to adenocarcinomas. The classification is based on the main histological criterion.

Tubular adenocarcinoma is the most frequent type of an EGC and tends to shape polypoid and fungating formations. Its tubules are very heterogeneously formed, and it is associated with inflammation and mucus histologically. Papillary adenocarcinoma is also very prevalent in EGC and more present in older patient. It shows epithelial cells with a fibrovascular center and is affiliated with higher rates of metastases and lymph node involvement. Mucinous adenocarcinomas on the other hand are characterized by its large portion of mucus arranged in pools and responsible for at least half of its volume. They constitute for about 10% of gastric carcinomas and display glands in inconsistent agglomerations with some sporadic signet ring cells. The poorly cohesive carcinomas contain signet ring cell carcinomas and typically consist of a mixture of those two cell types: signet ring cells and non-signet cells like lymphocytes, plasma cells or histiocytes. These tumors can vary greatly in shape and its components but can include microtrebaculae, defective glands or an ulcerated surface(Hu et al., 2012).

The WHO classification also lists types that very rarely occur like adenosquamous carcinomas, squamous cell carcinomas, choriocarcinoma, carcinosarcoma, parietal cell carcinoma, malignant rhabdoid tumor and many others. This detailed listing of numerous rare malignancies and thereby its impractical application has also been one of the main points of criticism over the last years(Hu et al., 2012).

There are other classifications, like the Ming or Gosseski classification, but the Lauren and the WHO classification are still the most common classifications in use. The inconsistent in prognosis as well as the difficulty in assigning malignancies to certain groups show need for a new classification system.

iv. Molecular classification

In 2014 a new classification of GC was introduced based on a molecular evaluation by The Cancer Genome Atlas (TCGA)(Bass et al., 2014). The molecular classification separated GC

into four subtypes: Epstein-Barr virus positive (EBV+), microsatellite instable (MSI), chromosomal unstable (CIN) and genomically stable. EBV+ showed repeated PIK3CA mutations, amplifications of the gens CD274 (or also recognized as programmed cell death 1 ligand 1 or PD-L1), JAK2 and PDCD1LG2(also known as programmed cell death 1 ligand 2 or PD-L2), and a very high DNA (Deoxyribonucleic acid) hypermethylation. EBV+ patients more likely to be male and located in the gastric fundus. MSI were associated with hypermutation including proteins in signalling by oncogenes that are targetable, like PIK3CA, ERBB3, ERBB2 and EGFR but only to a very small degree. Patients with MSI tumours were mostly older and female. MSI tumours also displayed hypermethylation, especially in MLH1. Most of the tumours were genomically stable (56%), showed diffuse histology and some mutations in CDH1 and RHOA, as well as CLDN18-ARHGAP fusions. CIN were mainly characterized by intestinal histology and TP53 mutations, as well as RTK-RAS activation(Bass et al., 2014).

One year later in 2015 the Asian Research Cancer Group(Cristescu et al., 2015) describes four subtypes of GC as, well but attempted to connect the subgroups closer to clinical outcome. The four following subtypes were described: Mesenchymal-like type, which showed the worst prognostic outcome and the highest recurrence rate, MSI with the best outcome in both recurrence and prognosis, and TP53-active and TP53-inactive subtypes, both with values in between the other two.

Generally, these molecular classifications still have to show their prognostic and therapeutic value as only two subtypes, EBV+ and MSI GC subtypes display clinical significance. Nowadays mainly histopathological classifications, especially the Lauren classification, are still most frequently used. These different classification types have several converging subtypes, which are shown in Figure 2 from Smyth et al.(Elizabeth C. Smyth et al., 2020)

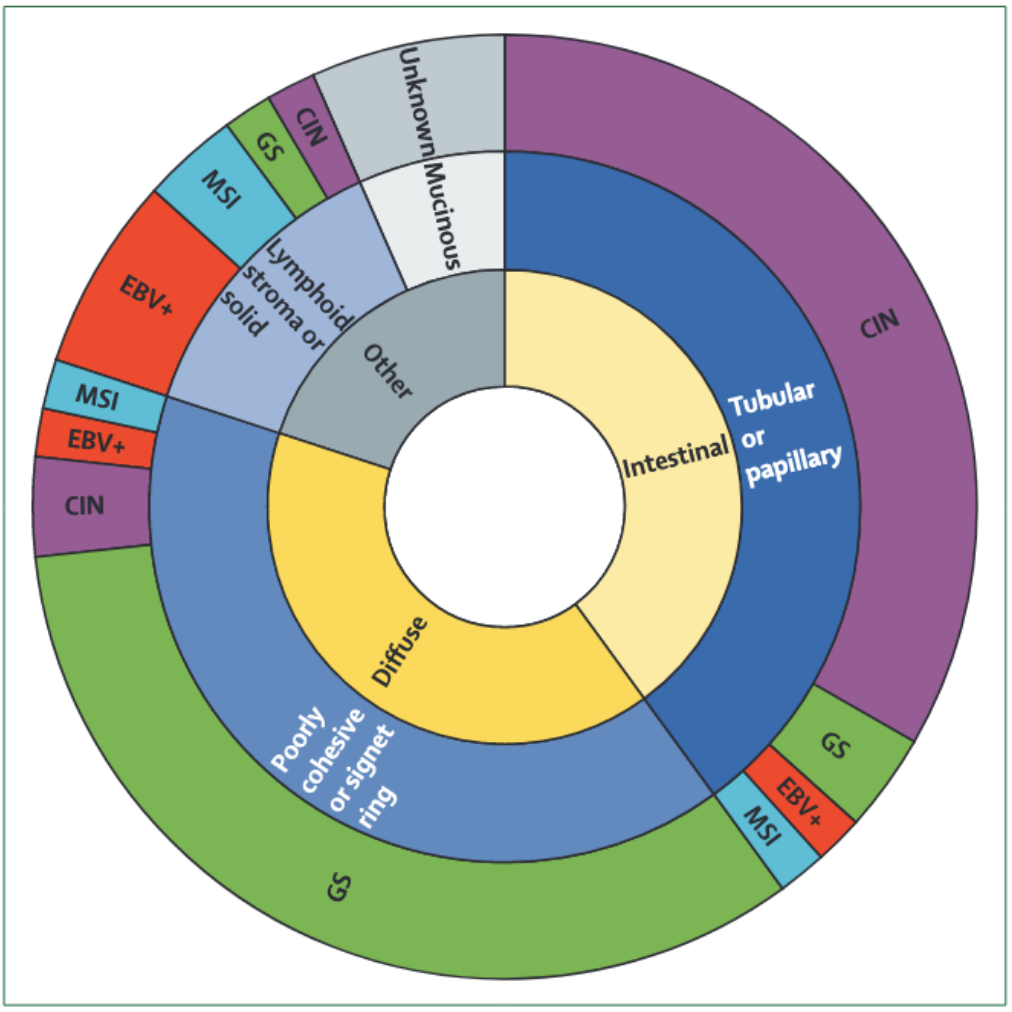


Figure 2 Graphical depiction of overlapping classifications by Smyth et al. (Elizabeth C. Smyth et al., 2020)

2.1.6 Symptoms and diagnosis

Symptoms often occur only at a late stage of disease and can vary. It can range from simple signs of indigestion, also called dyspepsia, unspecific abdominal pain, undefined weight loss or anorexia to dysphagia and regurgitation. It can lead up to anemia caused by internal bleeding in the stomach.

GC is usually diagnosed by an endoscopy, which allows to identify its macroscopic pattern, its location in the stomach and to take a biopsy for further histopathological classification. After diagnosis tumours should be staged and be reviewed by a multidisciplinary tumour board according to the last guidelines from the Union for International Cancer Control and American Joint Committee on Cancer(E. C. Smyth et al., 2016).

i. UJCC and TMC Staging

The stage of tumour should be documented by the TNM guidelines of the American Joint committee on Cancer (AJCC)/Union for International Cancer Control (UICC). The TNM staging of tumor was first introduced by Pierre Denoix(Denoix, 1952). The latest update has been published in 2017(Amin et al., 2017). The staging is based on three steps. The first letter ‘T’

stands for ‘tumour’ and is followed by a number between 1 and 4 to describe the size and the infiltration level of the tumour, as there are 5 layers of gastric tissue:

- *Mucosa*, the innermost layer, where almost every stomach cancer origin from;
- the *submucosa* follows next, which is a supportive tissue under the *mucosa*;
- the next layer is called *muscularis propria* and consists of muscle tissue that makes it possible to move its content and mix it with gastric fluids;
- followed by the *subserosa* and
- the *serosa*, which are the outer layers of the gastric separating it from the other organs in the abdomen and supporting its shape.

The next letter ‘N’ stands for lymph nodes and describes how far the cancer has spread to the surrounding lymph nodes and how many are affected.

The category ‘M’ stands for ‘metastasis’ and explains how far and if the tumour has already progressed to other and more distant parts of the body. Most common locations for metastasis are the lung or the liver. Table 1 shows the definitions of each category and Table 2 shows the possible constellations and their further division into the UJCC categories I – IV.

Table 1 TNM staging of gastric cancer according to the AJCC, 8th edition from Smyth et al.(E. C. Smyth et al., 2016)

Primary tumour (T)		Regional lymph nodes (N)		Distant metastasis (M)	
TX	Primary tumour cannot be assessed	**NX**	Regional lymph node(s) cannot be assessed	**M0**	No distant metastasis
T0	No evidence of primary tumour	**N0**	No regional lymph node metastasis	**M1**	Distant metastasis or positive peritoneal cytology
Tis	Carcinoma *in situ*: intraepithelial tumour without invasion of the lamina propria	**N1**	Metastasis in 1–2 regional lymph nodes		
T1a	Tumour invades the lamina propria or the muscularis mucosae	**N2**	Metastasis in 3–6 regional lymph nodes		
T1b	Tumour invades the submucosa	**N3**	Metastasis in 7 or more regional lymph nodes		
T2	Tumour invades the muscularis propria	**N3a**	Metastasis in 7–15 regional lymph nodes		
T3	Tumour penetrates the subserosal connective tissue without invasion of the visceral peritoneum or adjacent structures	**N3b**	Metastasis in 16 or more regional lymph nodes		
T4	Tumour invades the serosa (visceral peritoneum) or adjacent structures				
T4a	Tumour invades the serosa (visceral peritoneum)				
T4b	Tumour invades adjacent structures				

Table 2 AJCC Staging Classification, 8th Edition from In et al. (In et al., 2017)

Stage	T	N	M
IA	T1	N0	M0
IB	T2	N0	M0
	T1	N1	M0
IIA	T3	N0	M0
	T2	N1	M0
	T1	N2	M0
IIB	T4a	N0	M0
	T3	N1	M0
	T2	N2	M0
	T1	N3a	M0
IIIA	T4b	N1	M0
	T4a	N1	M0
	T4a	N2	M0
	T3	N2	M0
	T2	N3a	M0
IIIB	T4b	N1	M0
	T4b	N2	M0
	T4a	N3a	M0
	T3	N3a	M0
	T2	N3b	M0
	T1	N3b	M0
IIIC	T4b	N3a	M0
	T4b	N3b	M0
	T4a	N3b	M0
	T3	N3b	M0
IV	Any T	Any N	M1

These categories are mainly for prognostic purposes and provide information about survival rates. An estimate for survival rates according to the new edition of the AJCC TNM staging system for gastric cancer is displayed in Figure 3 with a Kaplan-Meyer diagram. The 5-year survival rate varies greatly for the different stages: It is higher for the stages IA (81.0% with a median survival of 129.8 months; 95% CI: 129.81-133.03) and IB (68% with a median survival of 112.8 months; 95% CI: 100.03 - /) and drops drastically to lower rates to the stages IIIC (8.3% with a median survival of 11.8 months; 95%CI: 10.87-12.68) and IV (5.6% and 8.9 months of median survival; 95% CI: 8.31-9.72)(In et al., 2017). These survival rates are very low compared to other cancer entities, especially because most of the cases are diagnosed at advanced stages. About 77% of the cases for men and 70% for women are initially diagnosed at stage II or IV(RKI, 2021), as GC doesn't show little to no distinct symptoms and is often

diagnosed if the tumour has already progressed to other organs or shown severe symptoms like anemia or internal bleeding.

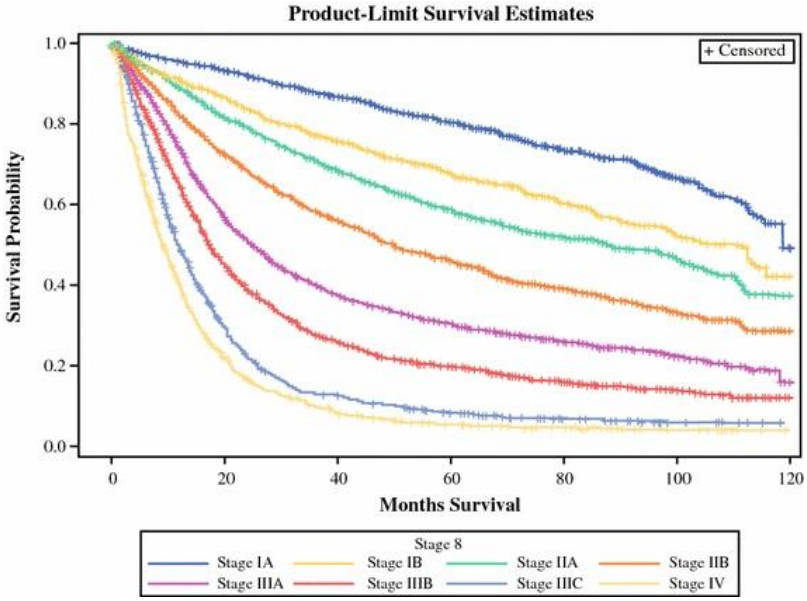


Figure 3 Survival estimates for gastric cancer for stage groupings when applied to the NCDB cohort from In et al. (In et al., 2017)

i. Diagnostic resources

As already mentioned, an endoscopy is mostly the standard procedure for diagnostics when a GC is suspected. But there are numerous other diagnostic possibilities too of which some of them are standard procedure to being able to stage a GC. There is the procedure of a full blood count to exclude or confirm the possibility of an anaemia based on an iron deficiency caused by a lack of intrinsic factor due to damaged gastric tissue. It is also important to test the renal and liver function to decide which treatment options are suitable. The endoscopic evaluation as well as a biopsy help to acquire samples for diagnosis, histopathological classification, and molecular biomarkers, like an existence of HER-2 amplifications to assess further treatment options. A computed tomography (CT) of the abdomen, chest and in some cases the pelvis is necessary to stage the tumour and specify the progress of the tumour. An endoscopic ultrasound (EUS) gives a more accurate assessment of the extent of the primary tumor and affected lymph nodes in case the malignancy might be operable. Additionally, a laparoscopy and a positron emission tomography (PET) helps to identify occult metastasis if in doubt. All these diagnostic steps contribute to compose a better idea of the extent of the disease and provides a range of possible therapies which then can be discussed in a multidisciplinary tumour board.

2.1.7 Therapy and management of GC

The European Society for Medical Oncology (ESMO) clinical practice guidelines for gastric cancer(E. C. Smyth et al., 2016) expresses that treatment planning in a multidisciplinary board

before the initiation of treatment is mandatory. The team should be composed of surgeons, radiologists, pathologists and medical as well radiation oncologists with further possible members. The design of the treatment plan and possibilities is closely connected to the extent and progression of the malignancy. Therefore, it is subdivided to management of a local or locoregional disease and into management of advanced or metastatic GC. For a better understanding for general treatment recommendations Table 3 shows the levels of evidence and the grade of recommendation.

Table 3 Levels of evidence and grades of recommendation adapted from Smyth et al (2016).(E. C. Smyth et al., 2016), who adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System(Dykewicz, 2001)

Levels of evidence	
I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, expert's opinions
	Grades of recommendation
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, ...), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

Management of local/locoregional GC

For any local or limited to just local and regional infiltration, surgical resection is still a valuable treatment option and can even be potentially curative. With higher penetration of the GC the treatment plan gets more complex and therapies like perioperative chemotherapy and adjuvant

treatments are included(E. C. Smyth et al., 2016). The treatment algorithm for local and reagional GC is shown in Figure 4.

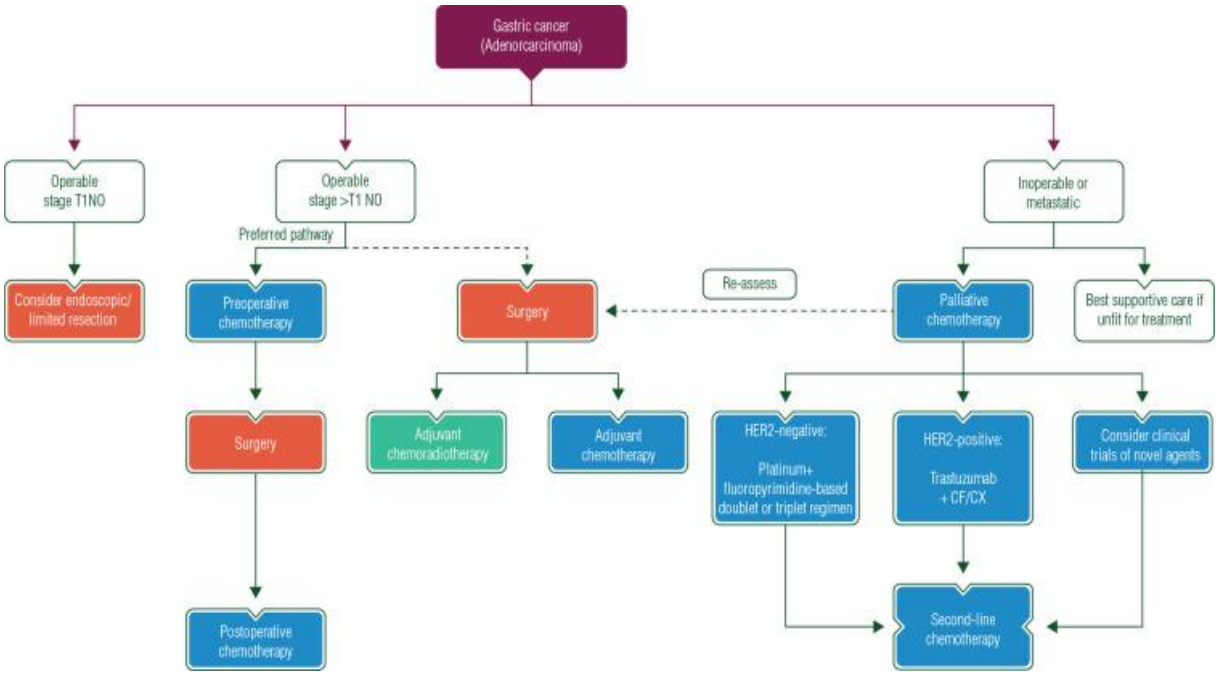


Figure 4 Gastric cancer treatment algorithm by Smyth et al. (2016)

a) Surgery

Surgical resection is still a big part of treating GC, especially in a local or locoregional extent. In Stage IA surgical resection is even potentially seen as a single intervention without the need for additional therapies. A single endoscopic resection is possible for a gastric cancer of Stage IA, if it is smaller than 2cm, non-ulcerated and well-differentiated [III, B]. There are two potential resection methods. An endoscopic submucosal dissection (ESD) is normally the standard procedure for most gastric cancer and the endoscopic mucosal resection (EMR) is only practicable if a malignancy is smaller than 10-15mm.

At Stage IB and higher a radical gastrectomy is preferred as a margin of at least 5cm is suggested between the tumor and the gastroesophageal junction (GEJ) and at least 8cm for diffuse tumor tissue [III, A]. There are different techniques due to the location of the tumor. If it is restricted to the proximal or distal part of the stomach and there is sufficient tissue intact, there is the possibility of a distal gastrectomy with the distal two thirds of the stomach removed and a connection between the proximal stomach and the small bowel or a proximal gastrectomy with the distal two thirds of the stomach detached. At total gastrectomy on the other hand removes the whole stomach with an anastomosis between the esophagus and the smaller bowel. There are different reconstructions methods.

There is debate on whether a distal or a total gastrectomy has a better outcome for middle and lower-third gastric cancer. Studies that have focused solely on long-term survival and

incidences of recurrences have mainly advised on total gastrectomy(Clark et al., 2006; Stein, Sendler, & Siewert, 2002), but if the focus is on quality of life and intraoperative complications were taking into consideration a distal gastrectomy was preferred(S. S. Lee, Chung, Kwon, & Yu, 2016; S. Park, Chung, Lee, Kwon, & Yu, 2014). The latest meta-analyses concludes in their review that distal gastrectomy should be preferred as it has better short-term and similar long-term outcomes as total gastrectomy(Z. Li, Bai, Xie, & Zhao, 2018).

There are various reconstructions methods for the total gastrectomy with basically two main distinctions: preserving the duodenal passage or surgery without the preservation. The most common surgery maintaining the passage is the jejunal interposition either including a reservoir or not. On the other hand, the standard technique for reconstruction without protecting the duodenal passage is the Roux-en-Y surgery, which is a gastric bypass constructing a pouch which is then connected to the small intestine. Generally, the Roux-en-Y eso-jejunostomy is the most practiced procedure as it's an uncomplicated procedure with an adequate nutritional result(Naum, Bîrlă, Marica, & Constantinoiu, 2020).

After a distal gastrectomy there are overall five options for reconstruction, Billroth I, Billroth II, Billroth II Braun, Roux-en-Y and an uncut Roux-en-Y. Billroth I and II are mostly performed in the Asian and Pacific region, while the Roux-en-Y reconstruction is preferred in Europe and Northern America. On the one hand Billroth I is an anastomosis of the remaining stomach to the duodenum, Billroth II on the other hand connects the stomach with the Jejenum while the cut end of the stomach as well as the duodenum are closed. These two techniques conserve the intestinal flow. The Roux-en-Y reconstruction changes the intestinal anatomy and is a more difficult procedure. But in general no superiority of an of those procedures were found in a recent meta-analyses for 30-day mortality, anastomotic stricture or leak and overall complications(Lombardo et al., 2022).

Proximal gastrectomy belongs to the new techniques that preserve the function of the pylorus and thereby avoid abrupt bolus passage, which is a common side effect of gastrectomies and could lead to dumping syndrome and weight loss. The pylorus protecting procedures are the so called 'pylorus-preserving gastrectomy' (PPG) and the 'proximal gastrectomy' and showed encouraging results in T1 cancers, which were not favorable for endoscopic resection(Nunobe et al., 2007; D. J. Park et al., 2008). There are different techniques for a proximal gastrectomy like a double tract reconstruction, a jejunal pouch interposition, a jejunal interposition, esophagogastrostomy and the double flap technique. Methods vary in their incidence of reflux esophagitis, anastomotic leak, anastomotic stricture, operative time, blood loss and hospital length of stay, but there no superior method has been identified. The doble flap technique has shown to decrease the risk of complications, but there is a need for larger randomized trials(Shaibu, Chen, Mzee, Theophilus, & Danbala, 2020).

Another surgical approach is the laparoscopic surgery especially the laparoscopic distal gastrectomy. Trials have shown so far that it is not inferior in overall survival (OS)compared to an open distal gastrectomy(H. J. Lee et al., 2019; van der Wielen et al., 2021). The KLASS-02 trial(H. J. Lee et al., 2019) even demonstrated less morbidity, less postoperative pain, as well as a shorter duration of hospital stays in contrast to patients who underwent an open distal gastrectomy. Trials are still required to confirm these results and show similar results for total gastrectomies, but laparoscopic surgeries are on the rise (E. C. Smyth et al., 2016).

b) Lymphadenectomy

There is still a debate about lymph node resection and if whether a D1 resection, which is limited to the perigastric lymph nodes, or a D2 resection, which includes all perigastric lymph nodes as well as lymph nodes at the left gastric, splenic, and common hepatic arteries and the coeliac axis, should be recommend. But generally, there is agreement that medically stable and fit patients should be subjects to a D2 resection in western countries and be mainly treated in specialized, high-volume centers [I, B]. Thereby the morbidity (15%) and mortality (3%) rates are made consistent including a specific recovery program(t. I. G. C. S. Group, 2013).

At Stage IB and higher a combined therapy is recommended due to a higher probability of relapses, recurrences, and metastases. However, a surgical resection for a T2-T4a gastric cancer with any lymph node status, as well as any clinically staged T1 lymph node positive tumor is still the main therapy if there are no distant metastases.

c) Perioperative and neoadjuvant chemotherapy

In general, perioperative chemotherapy is recommended for patients with a Stage IB or higher resectable GC with FLOT regime (fluorouracil, leucovorin, oxaliplatin, docetaxel). These findings are based on different trials over time. First the UK MRC MAGIC trials showed a better 5-year survival rate in favor for perioperative EFC (epirubicin, cisplatin and 5-fluorouracil) chemotherapy compared to surgery alone(David Cunningham et al., 2006). Then other trials displayed comparable findings with cisplatin and 5-fluorouracil (Ychou et al., 2011)(5-FU) and a capecitabine-containing study with a regime of epirubicin, cisplatin and capecitabine (ECX)or even oxalipatin instead of cisplatin(D. Cunningham et al., 2008). Then a series of studies investigating the FLOT regime were introduced in Germany. The studies compared the FLOT regime to the ECF/X regime in patients with locally advanced, resectable GC/EGJ cancer with longer over survivals of 50 months compared to 35 months favoring the FLOT regime(S.-E. Al-Batran et al., 2019; Pauligk et al., 2015). In a conclusion the FLOT regimen is recommended as the standard perioperative therapy for patients with resectable stage II and III gastric or gastroesophageal junction adenocarcinoma, according to 2022 ESMO guidelines for very fit candidates(Lordick et al., 2022). For other patients a pre- and postoperative chemotherapy with a platinum/fluoropyrimidine combination is preferred with equals outcomes for oxaliplatin and cisplatin(Lordick et al., 2022) [I, A].

d) Chemoradiotherapy

Radiotherapy as an additional element to chemotherapy as a so called chemoradiotherapy is still point of debate. Several trials have shown that there is no better overall survival with an additional radiotherapy after a gastrectomy with an adequate lymphadenectomy (more than D1 or D2)(Cats et al., 2018; J. Lee et al., 2012). If the Lymphadenectomy is lower than D1 or D2 or with an incomplete resection (R1) show a possibility for improving the overall outcome (Macdonald et al., 2001; Stiekema et al., 2015). Results from two more trials, are expected. The TOPGEAR trial, a phase III trial investigation perioperative ECF either including chemoradiation or without it, assessed its safety so far(Leong et al., 2017). The CRITICS II trial is a multi-centre phase II study and compares three different treatment options: chemotherapy, chemotherapy followed by chemoradiotherapy and chemoradiotherapy(Slagter et al., 2018). A preoperative chemoradiotherapy is thereby a treatment possibility for patients already receiving perioperative treatment, but on a category 2B based recommendation, meaning based on lower-level evidence(Joshi & Badgwell, 2021).

Management of advanced/metastatic cancer

Treatment of metastatic or locally advanced unresectable GC is mainly depending on the status of a patient and their accompanying diseases. Generally, chemotherapy improves survival and quality of life in those patients up to one year as median survival range compared to supportive care alone (median survival ranges from three to four months). The therapy range includes various cytotoxic agents like fluoropyrimidines, taxanes, platinum and irinotecan. Combining different regime generally results in higher response rates and enhanced survival in contract to single-agent therapies. First line chemotherapy treatment consists of a doublet of platinum and fluoropyrimidine(Ajani et al., 2016; Muro et al., 2019). A phase III trial, which compared oxaliplatin and cisplatin as well as capecitabine and fluorouracil, showed that cisplatin and oxaliplatin and capecitabine and flourouracil are equally efficient, there are differences in varieties of side effects though. Cisplatin is considered to cause more renal dysfunction and thromboembolic conditions and Oxaliplatin on the other hand is correlated to diarrhea and neuropathic disorders. Capecitabine however is related to a higher rate of hand-foot syndrome and neutropenia, which can be reduced through better patient education(D. Cunningham et al., 2008). Epirubicin is generally not used for advanced or metastatic gastric cancer in current regimens (D. Cunningham et al., 2008) . In older and frail patients, a reduced-intensity chemotherapy showed equal efficacy and similar survival rates with a better patient experience(Hall et al., 2021). In very fit patients, who consent to higher toxicity, can undergo a triple regimen existing of fluoropyrimidine, oxaliplatin and docetaxel with higher response rates and better progression free survival (S. E. Al-Batran et al., 2013). On the other hand, a single treatment strategy for very unfit patients can also be considered with either fluoropyrimidine,

taxane or irinotecan. Additionally, patients should be checked for their HER2 status and their PD-L1 combined positive score (CPS). If a HER2 or ERBB2 overexpression or amplification is discovered, trastuzumab should be added to the regimen of first line chemotherapy and if a PD-L1 over 5 is detected. For patients with advanced or metastatic HER2-negative gastric cancer and if a PD-L1 CPS of 5 or higher is detected, the addition of nivolumab to chemotherapy is now recommended as first-line therapy, based on CheckMate 649 results. Moreover Ramucirumab, either as monotherapy or in combination with paclitaxel, continues to be an option in the second-line setting, supported by RAINBOW and REGARD trials(Fuchs et al., 2014; Wilke et al., 2014). Further discussion will follow at a) Targeted therapies in GC and 2.2. Targeted therapies. An overview of the treatment algorithm is shown in Figure 5.

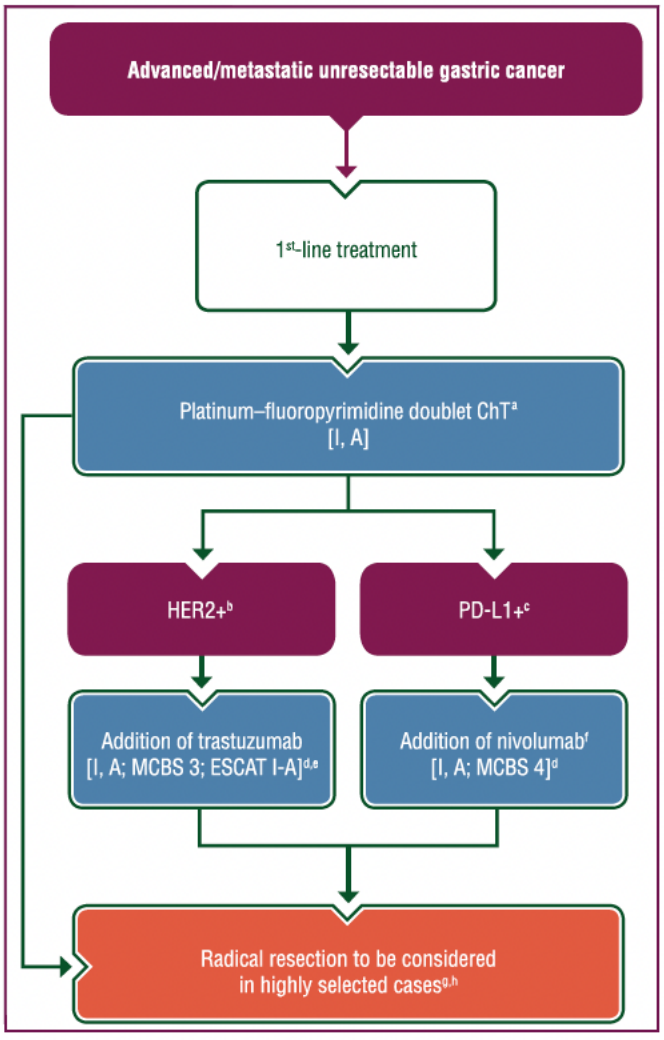


Figure 5 Treatment algorithm for first-line treatment of advanced/metastatic, unresectable gastric cancer by Lordick et al. (2022)

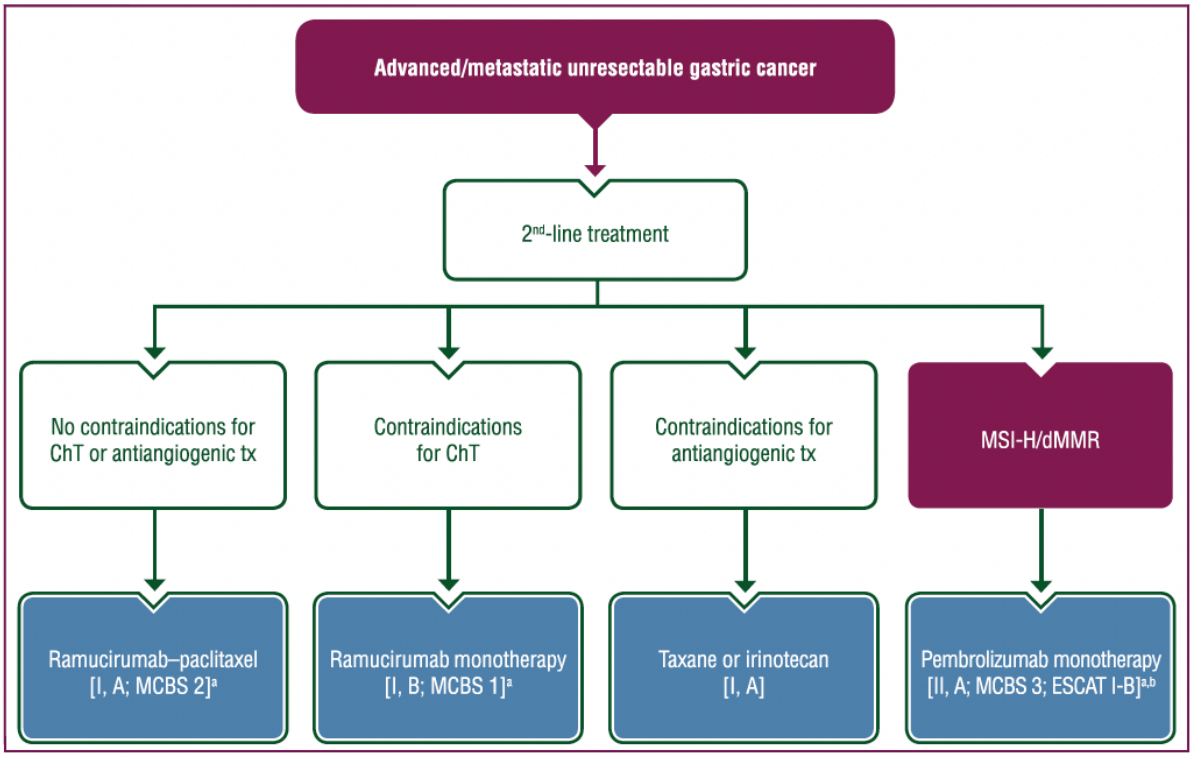


Figure 6 Treatment algorithm for second-line treatment of advanced/metastatic unresectable gastric cancerLordick et al. (2022).

Chemotherapy, that hasn't already been used in first-line treatment, can be employed in second line treatment.

a) Current targeted therapies in GC

There are currently three targeted therapies approved by the FDA for gastric cancer. Trastuzumab was the first targeted therapy approved for gastric cancer targeting human epidermal growth factor receptor 2 (HER2 or also known as ERBB2). HER2 is a protooncogene encoding for a tyrosine kinase, which is participating in several signal transduction processes that cause cell proliferation and differentiation. HER2 can be overexpressed and lead to increased proliferative signaling in the cell, as well as negatively influencing apoptosis induction. HER2 overexpression was first discovered in breast cancer but has also been investigated in other cancer entities like colorectal cancer, lung cancer, ovarian cancer, or prostate cancer. It's overexpression in stomach cancer patients ranged from 6% to 30% in different studies(Apicella et al., 2017), but is considered to be existing in around 20% of gastric cancer patients. In general, a HER2 overexpression or amplification in gastric cancer has shown to be a negative prognostic factor and is tested before the implementation of treatment in advanced gastric cancer patients. It can be assessed using different methods like immunohistochemistry (IHC) or in situ hybridization, determining if a HER2 antibody therapy is applicable. Ideally at least five biopsy specimens are taken from the proximal part of the malignancy and if possible, samples should be extracted from primary as well as metastatic sites(Angela N. Bartley et al., 2016; Tominaga et al., 2016). The monoclonal antibody directed

against HER2 is called trastuzumab and blocks the dimerization of HER2 with other members of the HER family member(Abrahao-Machado & Scapulatempo-Neto, 2016). The exact mechanism of Trastuzumab is still in debate, but it showed in patients with HER2 overexpression among other indicators an increased overall survival (OS) and overall response (OR) in a phase III clinical trial(Bang et al., 2010), which lead to its approval as the first targeted therapy in GC by the US Food and Drug Administration (FDA) in 2010 in combination with chemotherapy. The treatment algorithm for HER2 overexpressing patients contains a therapy with trastuzumab and first-line chemotherapy succeeded by a trastuzumab maintenance monotherapy(Ajani et al., 2016; Muro et al., 2019). There are different distinctive elements about HER2 overexpression and its therapy, for example that there is a variety of HER2 expression and a deprivation of HER2 dependence after treatment with Trastuzumab(Pietrantonio et al., 2016; Seo et al., 2019). There are other HER2 targeted therapies in clinical trials like trastuzumab-deruxtecan, which showed promising results so far. It is a combination of a HER2 antibody, a tetrapeptide-based linker and a cytotoxic topoisomerase I inhibitor. It showed an increased overall with a median of 12.5 months in the group treated with trastuzumab deruxtecan vs 8.4 months in the group treated with chemotherapy (HR for death, 0.59; 95% CI, 0.39 to 0.88; p= 0.01)(Shitara et al., 2020). Treatment options like pertuzumab and trastuzumab-emtansine, which are applied in patients with HER2 positive breast cancer, haven't shown any effect in gastric cancer.

The second agent ramucirumab is a human monoclonal antibody against the vascular endothelial growth factor receptor 2 (VEGFR). VEGFR and VEGFR-2 transmitted signaling is closely linked to angiogenesis and an elevated tumor infiltration. Ramucirumab is a human IgG1 monoclonal antibody against VEGFR-2 and averts ligand binding as well as the activation of the following pathway. It showed in two different phase III clinical trials an increase in OS and progression free survival (PFS) towards placebo treatment as either a single agent(Fuchs et al., 2014) or in combination with paclitaxel as chemotherapy(Wilke et al., 2014). Ramucirumab, either as monotherapy or in combination with paclitaxel, continues to be an option in the second-line setting, supported by RAINBOW and REGARD trials.

Pembrolizumab, a monoclonal human antibody targeting the immune checkpoint of programmed cell death 1 ligand 1 (PD-L1), was the third targeted therapy approved by the FDA in 2019 based on the findings of the KEYNOTE-059 study(Bang et al., 2019). PD-L1 treatment is an immune checkpoint inhibition that restores antitumor immune response to cancer cells presenting PD-L1 as a protection against T-cell activation(Ghosh, Luong, & Sun, 2021). In cancer treatment PD-L1 expression has been suggested to be one of the biomarkers universal for all cancers. The combined positive score (CPS) or the tumor proportional score (TPS) are still in debate over its prognostic value due to comparatively lower response rates

in gastric cancer, but generally a cut-off at a CPS score of 1 or higher lead to an increased OS and PFS(Xie et al., 2021).

In 2021 the combination of pembrolizumab and trastuzumab and fluoropyrimidine- and platinum-containing chemotherapy was approved by the FDA as a first-line treatment of patients with locally advanced unresectable or metastatic HER2 positive gastric and gastroesophageal junction adenocarcinoma based on the findings of an interim analysis of the phase III clinical KEYNOTE-811 trial(Janjigian et al., 2021). The integration of PD-L1 inhibitor into the HER2 positive regimen permits a pre-existing immune response to tumor antigens to unfold. In preclinical studies dendritic cells have shown to uptake HER2 antibody and present HER2 increasingly(Gall et al., 2017). This activates HER2-specific T cells that support anticancer activity with an extended immune response(S. Park et al., 2010). Additionally, trastuzumab proliferates the expression of PD-1 and PD-L1, which results in an increased number of lymphocytes infiltrating cancer tissue and modified major histocompatibility complex II(Triulzi et al., 2019). After chemotherapy the departing cancer cells instigate a response by dendritic cells and can promote priming of CD8+ tumor-specific T cells, which all lead to an increased response to cancer cells. The KEYNOTE-811 trials displayed an improved objective response rate of 74% (95% CI, 66.2 – 81.6) in the group that was treated with pembrolizumab compared to the group ministered with a placebo with a rate of 52% (95% CI, 43.0 – 60.7). The median survival in the group with pembrolizumab was 10.6 months (range 1.1 to 16.5) versus 9.6 months (range, 1.4 to 15.4) in the placebo arm. In total a 22.7% improvement was observed in the group treated with pembrolizumab (95% CI, 11.2 – 33.7; p = 0.00006). Studies in earlier stages of gastric cancer are now on their way (e.g., NCT04510285).

2.2 Targeted therapies

Targeted therapies as an element of cancer treatment have only been existing for a few decades now. In 1992 first clinical trials were initiated with Trastuzumab, a monoclonal antibody targeting the epidermal growth factor HER2(Falzone, Salomone, & Libra, 2018). Today there are 155 targeted therapies approved by the FDA for the treatment against cancer(Daniel Alexander Hescheler et al., 2022).

Although targeted therapies have been introduced over 30 years ago, there have been struggles to find a definition generally. The U.S. National Cancer Institute outlines targeted therapies as “drugs or other substances that block the growth and spread of cancer by interfering with specific molecules (“molecular targets”) that are involved in the growth, progression and spread of cancer”(U.S. National Institute of Cancer, 2022). This definition includes the simplified explanation that a therapy that is directed against a molecular target equals a targeted therapy. But there are other aspects for a targeted therapy to be successful. Sledge (2005) comprehended the measurability, quantification, and validation in a clinical

setting to be an important part of a targeted therapy. Otherwise it couldn't be correlated to the clinical outcome of a treatment or the necessity couldn't be evaluated before the initiation of a treatment. Y. T. Lee, Tan, and Oon (2018) divided targeted therapies into different modes of action and types of molecular targets. The two main modes of action are either aiming at the tumor cells themselves or focus on the tumor environment. The different types of molecular targets include small molecules like tyrosine kinase inhibitors, monoclonal antibodies, cancer vaccines and gene therapies.

Mendelsohn, Gray, Howley, Israel, and Thompson (2014) described targeted therapies as the use of "an agent (or a combination of agents) that acts with a high degree of specificity on a well-defined targeted or biological pathway that drives that cancer phenotype, so that when a patient is treated, there is destruction of cancer cells, with minimal harm to normal cells". This interpretation focuses on the minimal damage on other than tumor cells, which is an important differentiation to chemotherapy. It also includes elements of pathways in general that power a malignancy. As a conclusion the following pillars of a definition for targeted therapies in cancer treatment have been accumulated:

- A well-defined target or biological pathway that constitute a certain kind of cancer,
- a target that is measurable in a clinical setting to identify patients who benefit from treatment as well as monitor progress (availability of biomarkers),
- minimal damage to non-cancer cells and thereby a high specificity to malignant cells,
- treatment is restricting growth, differentiation or proliferation of cancer cells or their environment.

2.2.1 Biomarkers in oncology

Biomarkers are objectively measurable characteristics that indicate normal biological processes, pathogenic processes, or responses to an intervention. In oncology, they are commonly categorized as diagnostic biomarkers to classify or confirm a disease, prognostic biomarkers to estimate outcome independent of treatment, and predictive biomarkers to estimate the likelihood of response to a specific therapy (FDA-NIH Biomarker Working Group, 2016).

Biomarkers are relevant both for patient stratification and for linking targeted therapies to molecular alterations. In routine oncologic practice, biomarker assessment commonly relies on immunohistochemistry (IHC) for protein expression, fluorescence in situ hybridization (FISH) for gene amplification or rearrangements, and DNA-based methods (e.g., targeted sequencing or next-generation sequencing) for mutations and copy number alterations (FDA-NIH Biomarker Working Group, 2016).

1. Immunohistochemistry (IHC)

IHC is widely used to assess protein expression in tumor cells and the tumor microenvironment. It is accessible in routine pathology and enables interpretation within histologic context. In the setting of gastric cancer, IHC is frequently applied to determine protein-based biomarkers that guide treatment decisions and trial eligibility(A. N. Bartley et al., 2017; Lordick et al., 2022).

2. In situ hybridization (ISH), including fluorescence in situ hybridization (FISH)

ISH/FISH methods assess gene amplification or copy-number alterations directly in tumor tissue. These methods are frequently used in oncology when gene-level confirmation is required, especially when protein expression results are equivocal or when amplification status is directly relevant to therapy selection (A. N. Bartley et al., 2017).

3. DNA sequencing and next-generation sequencing (NGS)

DNA-based methods including targeted panels and broader NGS approaches allow detection of mutations, copy-number changes, and other genomic alterations across multiple genes simultaneously. These approaches are increasingly important as trial portfolios expand and as more therapies target specific genomic features. Sequencing-based profiling also supports trial matching, especially in biomarker-driven umbrella and basket designs(FDA-NIH Best Working Group, 2016; Lordick et al., 2022).

A recurring challenge in biomarker-guided oncology is the heterogeneity of tumors, including intra-tumoral heterogeneity and differences between primary and metastatic sites, which can affect biomarker expression and assay results. In addition, differences in assays, scoring systems, and cut-offs across studies can complicate cross-trial comparison and clinical generalizability, which is an issue that is particularly relevant for biomarkers commonly used in gastric cancer research and clinical trials(A. N. Bartley et al., 2017; Lordick et al., 2022).

2.2.2 Different target types

There are options to further divide targets into different types according to the U.S. National Cancer Institute:

- Hormone therapies, which are aiming at tumors progression responsive to hormones. Therefore, they are either directed at keeping hormones with positive influence on tumor growth to a minimum or blocking hormone receptor interaction. So far, the FDA approved hormone therapies for prostate and breast cancer.
- Signal transduction inhibitors are a big part of molecular targeted therapies. Normally cells receive a signal externally which is then transduced via different pathways and control mechanisms to induce cell growth or division. In cancer cells these signaling pathways are altered in a way that they don’t need the external input anymore.

Therefore, signal transduction inhibitors interfere in the activities of signal transduction that lead to tumor growth, differentiation, or proliferation for example by blocking receptors or inhibiting kinases.

- Gene expression modulators influence proteins that regulate gene expression.
- Apoptosis inducers instigate a process of regulated cell death that is normally generated to dispose of abnormal or unnecessary cells. In cancer cells this process is being evaded by different methods and apoptosis inducer are attempting to reinstate this course.
- Angiogenesis inhibitors prevent the proliferation of blood vessel which is named angiogenesis and is important for tumor growth. There are different methods, either interfering in the blood vessel formation or their growth.
- Immunotherapies utilizes the body's own immune system to target cancer cells. There are also various techniques of the how to support the immune system to identify and attack cancer cells. One is to attach a antibody to the cancer cells surface.
- Toxin delivering molecules are targeting malignant cells specifically through an antibody that is combined with a toxic chemical or a radioactive therapeutic. They bind to the cancer cells via the antibody and then induce the toxic therapeutic into the cells.

In some cases, cancer vaccines and gene therapy are also regarded as targeted therapies but are not included in this review.

2.2.3 Targeted pathways

Targeted therapies aim mostly at a specific protein, gene, or other target. After initiation the reach of targeted therapies isn't limited to the target itself but has influence on various attached pathways and its precursors as well as successors. Effects on processes of a pathway that are proceed the target are called 'upstream' influence and succeeding impacts are combined as 'downstream' effects. Various significant signaling pathways were distinguished and the frequencies of their alteration in several cancer types. Pathways that are known as most regularly altered are for example the RTK/RAS/MAP- kinase pathway or the PI3K/Akt signaling(Vogelstein & Kinzler, 2004). Over the years information of these pathway modifications and interactions have been gathered in databases like Kyoto encyclopedia of genes and genomes (KEGG)(Kanehisa & Goto, 2000) or Pathway Commons(Cerami et al., 2011).

Pathway analyses are still a work in process and new insights are being published regularly but the Krypto Encyclopedia of Genes and Genomes (KEGG) database put together several pathways. There is a map of 'pathways in cancer' with several pathways that are up – or down-regulated in many different types of cancer. The pathways mainly identified in the KEGG map 'pathways in cancer' are (Figure 7):

- *Adherens junctions* are connections between epithelial cells that use different proteins. Proteins that have been associated with carcinogenesis are E-cadherin and β-catenin. E-cadherin has been associated as a tumor suppressor and thereby with apoptosis, cell cycle arrest, reduction of aggressiveness. E-cadherin loss has been linked to a reduced survival and poor prognosis for patients from different types of cancer and shown clinical importance on an epigenetic and genetic level(S. H. M. Wong, Fang, Chuah, Leong, & Ngai, 2018). β-catenin on the other hand is strongly linked to Wnt/β-catenin signaling pathway which enables processes like cancer stem cell renewal or cell differentiation and therefore is ubiquitous to a variety of malignancies. It has been a target of clinical research for a while now and new strategies(Y. Zhang & Wang, 2020).
- *Apoptosis* is regulated cell death of normal cells that are either experienced irreversible change or unneeded. It takes up a big part in pathological as well as physiological processes in a cell. Malignant cells have ways to avoid apoptosis and thereby it is a of high interest to research to identify techniques restore its function. Important examples of components of apoptosis are B-cell lymphoma 2 (Bcl-2) proteins which are among others, modulators of apoptosis and caspases which are crucial elements of programmed cell death. Molecular targets in trials are for example caspase inhibitors, Bcl-2 inhibitors and (X-linked) inhibitor of apoptosis protein (XIAP) inhibitors(X. Xu, Lai, & Hua, 2019).
- *Calcium signaling pathway* is responsible for various important cellular processes in regular cells, but also in cancer cells. The calcium ion ( ) is pivotal element of any cell's homeostasis, as well as induction of metabolic or proliferative processes and thereby a key part of carcinogenesis and maintaining proliferation and cell division. There are some certain genes like TRPM8 or TRPC6 for Ca^{2+} ion channels, which are overexpressed in different cancers like breast or lung cancer. These already have been targeted by inhibitors (for example SOR-C13 for TRPC6) in clinical trials(Roberts-Thomson, Chalmers, & Monteith, 2019).

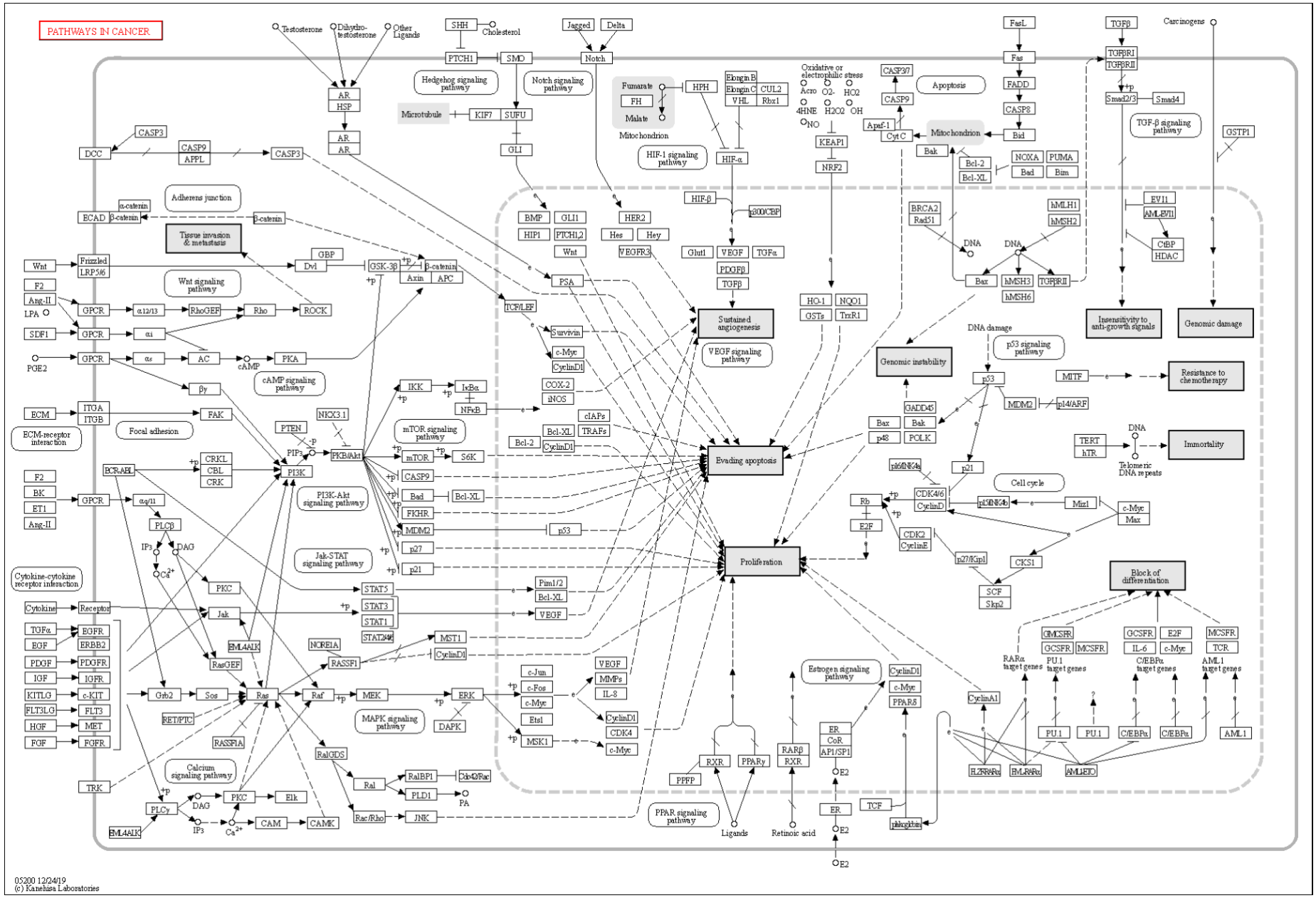


Figure 7 Pathways in cancer by Krypto Encyclopedia of Genes and Genomes (KEGG)(KEGG, 2022).

- *Cyclic adenosine monophosphate* (cAMP) *signaling pathway* is involved in transcription processes of numerous target genes predominantly through protein kinase A (PKA). It also has influences on a diverse set of other processes like cell growth, differentiation, apoptosis, cell metabolism, and ion channel activation(H. Zhang, Kong, Wang, Jiang, & Hua, 2020).
- *Cell cycle pathway* is affected in basically all tumor types and often originates carcinogenesis. There are several checkpoints and cellular functions in a cell cycle that are suitable as a target for cancer and therapies like cyclin dependent kinases 4 and 6 (CDK4/6). CDK4/6 are promoting cell growth and so their inhibition results in cell cycle arrest. There are also CDK inhibitors for kinases 1/2/3/5/7/9 in clinical trials(Suski, Braun, Strmiska, & Sicinski, 2021).
- *Cytokine-cytokine* interaction is the predecessor for the JAK-STAT pathway in cancer pathways. Cytokines are small proteins that are a crucial element of inflammation and cell survival processes. An example for a cytokine-cytokine interaction targeting is Interleukin 6 (IL-6) signaling with monoclonal antibodies in renal cell cancer (Rossi et al., 2010)
- *Extracellular matrix (ECM)-receptor* play a crucial part in the tumor environment and thereby have influence on the constantly changing surrounding of tumor cells. To be able to target it in the future a better molecular and physiological understanding is necessary at first(Mohan, Das, & Sagi, 2020).
- *Estrogen* receptors (ER) are involved in various processes like preservation of bone mass or conservation of blood vessel or the central nervous system. A disbalance in ER can lead to cancer precursors in uterine, ovarian and breast cells. In ER positive cancer tissues, which makes up to 70% of all breast cancers, ER signaling impels growth and therefore is a therapeutic target that has been taken advantage of. There are two different kinds of inhibitors for the ER pathway: a) therapies that reduce estrogen levels endogenously and b) drugs that target ER directly, which can be further divided into selective estrogen receptor modulators (SERMs) and selective estrogen receptor degraders (SERDs). There is already a wide spectrum of therapies in clinical use like tamoxifen and fulvestrant (Patel & Bihani, 2018).
- *Focal adhesion* and its kinase, focal adhesion kinase (FAK, gene name *PTK2*), characteristically are involved in signal transduction of cell adhesions and migration. It also a major impact of these features of cancer cells that are indispensable for growth. Therefore, FAK seems to be a great target for some varieties of cancer as FAK kinase inhibitors are being tested in clinical trials(Dawson, Serrels, Stupack, Schlaepfer, & Frame, 2021).

- The *Hedgehog* signaling pathway is a factor that has huge influence on development of vertebrates and its evolution by supporting a correct segregation of organs, limbs, and other aspects of these species especially in early development. Hedgehog signaling is also involved in a variety of steps in carcinogenesis in malignities like pancreatic or esophageal cancer. It is related to cell invasion and higher ability to proliferate and spread. Target gene examples are regulators of the cell cycle like CCNE1 and CCND2 and apoptosis regulator like BCL2, MYCN or PAX6/7/9. There are already some targeted therapies aiming at target genes related to the hedgehog signaling pathway, like hedgehog ligand inhibitors vismodegib or sonidegib and smo inhibitors taladegib(Skoda et al., 2018) .
- Hypoxia-inducible factor 1 (HIF-1) and the *HIF-1signaling pathway* induces transcription of various factors that are responsible for cell proliferation, invasion, and survival as well as glucose metabolism and angiogenesis. It can be overexpressed in malignant cells due to lack of oxygen or different genetic alterations and is affiliated with higher mortality rates and treatment failure. There are already small-molecule inhibitors of HIF-1 activity available (Albadari, Deng, & Li, 2019; Semenza, 2003).
- *Janus kinase-signal transducer and activator of transcription (Jak-STAT) signaling pathway* modulates nearly every immune process which includes cancer cell identification and avoidance of immune responses by malignant cells. As the Jak-STAT pathway is continuously being studied, its complexity appears to be overwhelming and targeting just one part of it. For now only STAT inhibitors are going through clinical trials with more research in preclinical studies on the way aiming at other angles(Owen, Brockwell, & Parker, 2019).
- *The mitogen-activated protein kinases (MAPK) pathways* are a crucial element of any cells signal transduction like cell survival, proliferation, differentiation, and metabolic reprogramming. MAPK is more understood as a cascade that consist of different pathways like rat sarcoma (RAS), rapidly accelerated fibrosarcoma (RAF) and extracellular signal-regulated kinase (ERK). An aberrant regulation of these kinases has been investigated in detail and many overexpressed or mutated targets in all varieties of cancer have been identified with therapies already in place or under way (Degirmenci, Wang, & Hu, 2020; Roberts & Der, 2007).
- *The mechanistic target of rapamycin* (mTOR) is a protein kinase that modulates cell survival, growth, immunity, and metabolism on various levels. Its de-regulation can cause many morbidities like obesity, Alzheimer's disease and various cancer entities like breast, liver, lung, prostate cancer. Although there is no distinctive biomarker on the benefit of mTOR inhibitor treatment there are already several therapies in clinical settings and more in trials(Hua et al., 2019).

- The *Notch signaling pathway* is perpetuated through evolution and performs an important part in the development of embryos and cell differentiation. However, studies also indicated a major role in the progression of malignant cells by an irregular activation, which makes it a target for treatment strategies. There are Notch-inhibitors in clinical trials, nevertheless they have shown a various range of adverse events and only modest efficacy so far(L. Li et al., 2017).
- TP53 (p53) is the gene that is altered the most frequent in human cancers with about 50% demonstrating a mutation in general and thereby an inevitable target for prospective drugs(Duffy, Synnott, & Crown, 2017). P53 is a tumor suppressor gene that typically establish a barrier to carcinogenesis and tumor proliferation. But if p53 is mutated, it is unable to keep its important role and reverses its function by promoting metastasis and invasion. For a long time p53 was thought to be undruggable, but there are p53 reactivators on the rise in clinical trials(Mantovani, Collavin, & Del Sal, 2019).
- The *phosphatidylinositol 3-kinase (PI3K)/protein kinase B (PKB/Akt) (PI3K/Akt) pathway* is responsible for vital parts of cell growth and cell survival. Its mostly activated dysregulation can be observed in a selection of malignities as a crucial factor for cell proliferation and invasion. So thereby inhibiting this pathway has been identified as a promising strategy that has instigated a variety of inhibitors(Chen, Law, & Loh, 2005; Fattahi, Amjadi-Moheb, Tabaripour, Ashrafi, & Akhavan-Niaki, 2020).
- *Poly(ADP-ribose) polymerase* (PARP) pathway regulates various processes like transcription, stabilization of transcriptional processes, DNA damage signaling, inflammation and metabolism. It especially regulates punctual and reliable restoration of DNA damage. Some malignant cells are highly dependent on this DNA damage repair mechanism and therefore an inhibition of PARP enzymes was effectively introduced as a targeted therapy for numerous cancer entities. Right now the obstacle of fast drug resistance is being studied, which occurs in some specific types of cancer(Dias, Moser, Ganesan, & Jonkers, 2021).
- The transforming growth factor β (TGF-b) signaling pathway is frequently dysregulated in many pathologies, just as in cancer. It normally induces a tumor suppressor activity that can lead to apoptosis, but its activation in advanced tumor cells can support carcinogenesis together with proliferation and invasion. As TGF-b has a binate function in different cells its inhibition as treatment is a complex strategy(Colak & Ten Dijke, 2017).
- The vascular endothelial growth factor (VEGF) is a vital element of regulating angiogenesis vascular endothelial cells and therefore an effective method for cancer cells to avoid hypoxia. It is an indispensable element for tumor growth and development. There are other pathways like platelet-derived growth factor (PDGFR)

and fibroblast growth factor (FGFR) that are closely linked to VEGFR. Inhibitors of elements of these pathways have been introduced to clinical settings successfully with further trials undergoing investigation(Carmeliet, 2005; Zhao & Adjei, 2015).

- *Wnt signaling* is a vital mechanism modulating processes like cell differentiation and proliferation, migration and apoptosis, which by irregulated activation can promote tumor development and proliferation of various malignancies. The Wnt pathway is strongly connected to beta-catenin and components of these pathways were identified as targetable. Drugs like PORCN or FZD inhibitors are in first clinical trials(Y. Zhang & Wang, 2020).
- *The base excision repair (BER) pathway* is part of the DNA damage response and cellular apparatus that mends impaired DNA in every part of the cell cycle. Among other enzymes like PARP1 have a role in base excision repair that are can be targeted in cancer cells that rely on these enzymes(Cleary, Aguirre, Shapiro, & D'Andrea, 2020).
- The Erbb receptor family consist of the epidermal growth factor receptor (EGFR or ErbB1/Her1), ErbB2/Her2, ErbB3/Her3 and ErbB4/Her4. EGFR and Her2 are one of the most targeted receptor kinases in targeted therapies for cancer. EGFR and Her2 overexpression are linked to poorer overall survival in various types of cancer and especially linked to breast, lung and ovarian cancer. It is closely in connection with the MAPK cascade but attached to many other pathways that instigate cell proliferation. There are Errb receptor inhibitors already approved as well as several new developed drugs in clinical trials, which have shown clinical success(Z. Wang, 2017).

Ras is considered a gene family consisting of the genes *KRAS*, *NRAS* and *HRAS* that is most frequently mutated in malignancies of all gene families. For a long time, it seems impossible to target any of member of the Ras family, but AMG 510 aiming at the mutation KRAS-G12C has been developed and even already approved by the FDA in 2021 in non-small-cell lung cancers. There are also several other drugs targeting *KRAS* and even *NRAS* being investigated(Moore, Rosenberg, McCormick, & Malek, 2020).

2.2.4 FDA approved targeted therapies

As already mentioned, there are 155 drugs targeting different types of cancer already approved by the FDA. These targeted therapies have different target genes and have certain indications and tumor entities for which their use was approved. Table 4 shows the names of the agents as well as their matching target genes, which was adapted from Hescheler et al. (Daniel Alexander Hescheler et al., 2022). The Table 4 shows all FDA approved targeted therapies up to date with the regarding target genes, mechanism of action according to the drug dictionary of NCI and cancer types they were approved for.

2.2.5 Clinical study phase

Clinical trials evaluating targeted therapies typically progress through four main phases, each designed to answer a specific set of questions regarding safety and clinical benefit. Phase I studies primarily assess safety, tolerability, and dose finding, which often includes dose-escalation designs, and may provide early signals of activity in small patient cohorts. Phase II trials expand evaluation to better characterize antitumor activity in a defined population and further refine safety, commonly using endpoints such as objective response rate and progression-free survival. Phase III studies are larger, comparative trials that test whether a new therapy improves clinically meaningful outcomes (e.g., overall survival, progression-free survival, quality of life) against the current standard of care, forming the basis for many regulatory approvals. Finally, Phase IV trials are conducted mostly after approval and focus on post-marketing safety, real-world effectiveness, long-term outcomes, and optimization of use in broader patient populations, including rare adverse events that may not be detected in earlier phases(Dal-Ré et al., 2023).

Table 4 Targeted therapies approved for clinical use by the FDA with matching target genes adapted from Hescheler et al.(Daniel A. Hescheler et al., 2020)

Drugs	Gene Targets
Abemaciclib	*ERBB2,ESR1,CDK4,CDK6*
Abiraterone	*CYP17A1*
Acalabrutinib	*BTK*
Afatinib	*ERBB2,EGFR*
Aldesleukin	*IL2RB,IL2RA,IL2RG*
Alectinib	*ALK*
Alemtuzumab	*CD52*
Alitretinoin	*RARA,RXRA,RARB,RXRB,RARG,RXRG*
Alpelisib	*ERBB2, ESR1, PIK3CA*
Amivantamab	*EGFR,MET*
Anastrozole	*CYP19A1*
Apalutamide	*AR*
Apatinib	*KDR,PDGFRB,SRC,RET*
Atezolizumab	*ALK, EGFR, CD274*
Avapritinib	*KIT,PDGFRA,*
Avelumab	*CD274*
Axicabtagene ciloleucel	*CD19*
Axitinib	*FLT1,FLT4,KDR*
Belantamab	*TNFRSF17*
Belinostat	*HDAC1,HDAC2,HDAC3,HDAC4,HDAC5,HDAC6,HDAC7,HDAC8,HDAC9*
Bevacizumab	*VEGFA*
Bexarotene	*RXRA,RXRB,RXRG*
Binimetinib	*BRAF,MAPK1,MAP2K2,*
Blinatumomab	*CD19*
Bortezomib	*PSMB5,PSMB1,*
Bosutinib	*BCR,ABL1,LYN,HCK,SRC,CDK2,MAP2K1,MAP2K2,MAP3K2,CAMK2G,*
Brentuximab	*TNFRSF8,*
Brexucabtagene Autoleucel	*CD19*
Brigatinib	*EGFR,ALK*
Cabozantinib	*KDR,MET,RET*
Capmatinib	*MET*
Carfilzomib	*PSMB10,PSMB2,PSMB9,PSMB1,PSMB8,PSMB5*
Cemiplimab	*PDCD1*
Ceritinib	*ALK*
Cetuximab	*KRAS,EGFR*
Cobimetinib	*BRAF,MAP2K1,BRAF*
Copanlisib	*PIK3CA,PIK3CD*
Crizotinib	*MET,NTRK1,ROS1,ALK*
Dabrafenib	*RAF1,BRAF*
Dacomitinib	*EGFR*
Daratumumab	*CD38,*
Darolutamide	*AR,PGR,*
Dasatinib	*ABL1,ABL2,DDR1,DDR2,EPHA2,FYN,KIT,LCK,PDGFRA,PDGFRB,SRC,YES1*
Denileukin	*IL2RA,IL2RB*
Denosumab	*TNFSF11*
Dinutuximab	*B4GALNT1*
Dostarlimab	*PDCD1*
Durvalumab	*CD274,CD80*
Duvelisib	*PIK3CG,PIK3CD*
Elotuzumab	*SLAMF7*
Enasidenib	*IDH2*
Encorafenib	*BRAF*
Enfortumab vedotin	*NECTIN4*
Entrectinib	*NTRK1,NTRK2,NTRK3,ROS1,JAK2,TNK2*
Enzalutamide	*AR*
Erdafitinib	*FGFR2,FGFR3,FGFR4,RET,PDGFRA,PDGFRB,KIT,KDR*
Erlotinib	*EGFR*
Everolimus	*MTOR*
Exemestane	*ESR1,CYP19A1*
Fedratinib	*JAK2,FLT3,JAK1*
Fostamatinib	*SYK*
Fulvestrant	*ESR1*
Gefitinib	*EGFR*
Gemtuzumab ozogamicin	*CD33,*
Gilteritinib	*FLT3,AXL,ALK*
Glasdegib	*SMO,*
Ibritumomab	*MS4A1*
Ibrutinib	*BTK*
Idecabtagene Vicleucel	*TNFRSF17*
Idelalisib	*PIK3CD*
Imatinib	*ABL1,KIT,PDGFRA,PDGFRB*
Infigratinib	*FGFR1,FGFR2,FGFR3,FGFR4*
Inotuzumab Ozogamicin	*CD22*
Iobenguane	*SLC6A2*
Ipilimumab	*CTLA4*
Isatuximab	*CD38*
Ivosidenib	*IDH1*
Lanreotide	*SSTR2,SSTR5*
Lapatinib	*EGFR,ERBB2*
Larotrectinib	*NTRK1,NTRK2,NTRK3*
Lenvatinib	*FGFR1,FGFR2,FGFR3,FGFR4,FLT1,FLT4,KDR,KIT,PDGFRA,PDGFRB,RET*
Letrozole	*CYP19A1*
Lisocabtagene Maraleucel	*CD19*
Loncastuximab	*CD19*

Drugs	Gene Targets
Lorlatinib	*ROS1,ALK*
lutetium Lu 177-dotatate	*SSTR1,SSTR2,SSTR3,SSTR4,SSTR5*
Margetuximab	*ERBB2*
Midostaurin	*KDR,PRKCA,FLT3*
Mogamulizumab	*CCR4*
Moxetumomab	*CD22*
Necitumumab	*EGFR*
Neratinib	*ERBB2,*
Nilotinib	*ABL1,KIT,*
Nintedanib	*KDR,PDGFRA,PDGFRB,FGFR1,FGFR2,FGFR3*
Niraparib	*BRCA1,BRCA2*
Nivolumab	*PDCD1*
Obinutuzumab	*MS4A1*
Ofatumumab	*MS4A1*
Olaparib	*BRCA1,BRCA2*
Olaratumab	*PDGFRA*
Osimertinib	*EGFR*
Palbociclib	*ERBB2,ESR1,CDK4,CDK6,*
Panitumumab	*KRAS,EGFR*
Panobinostat	*HDAC1,HDAC2,HDAC3,HDAC4,HDAC5,HDAC6,HDAC7,HDAC8,HDAC9*
Pazopanib	*FGFR1,FGFR2,FGFR3,FLT1,FLT3,FLT4,KDR,KIT,PDGFRA,PDGFRB,RET,TEK*
Pembrolizumab	*PDCD1*
Pemigatinib	*FGFR1,FGFR2,FGFR3,FGFR4*
Pertuzumab	*ERBB2*
Pexidartinib	*CSF1,KIT,FLT3*
Polatuzumab	*CD79B*
Ponatinib	*FGFR1,KDR,PDGFRA,SRC,ABL1*
Pralsetinib	*RET,DDR1,NTRK3,FLT3,JAK1,JAK2,NTRK1,KDR,PDGFRB,FGFR1,FGFR2*
Ramucirumab	*KDR*
Regorafenib	*ABL1,BRAF,EPHA2,FGFR1,FGFR2,FLT1,FLT3,KDR,KIT,NTRK1,PDGFRA,PDGFRB,FRK,RAF1,RET,MAPK11,TEK*
Ribociclib	*ERBB2,ESR1,CDK4,CDK6*
Ripretinib	*PDGFRA,KIT*
Rituximab	*MS4A1*
Romidepsin	*HDAC1,HDAC2,HDAC4,HDAC6*
Rucaparib	*BRCA1,BRCA2*
Ruxolitinib	*JAK1,JAK2*
Sacituzumab Govitecan	*TACSTD2*
Selinexor	*XPO1*
Selpercatinib	*RET,FLT1,FLT4,FGFR1,FGFR2,FGFR3*
Selumetinib	*MAP2K1,MAP2K2*
Siltuximab	*IL6*

Drugs	Gene Targets
Sipuleucel-T	*ACPP*
Sonidegib	*SMO*
Sorafenib	*ABL1,ARAF,BRAF,FGFR1,FGFR2,FLT1,FLT3,FLT4,KDR,KIT,PDGFRA,PDGFRB,RAF1,RET*
Sotorasib	*KRAS*
Sunitinib	*CSF1R,FGFR1,FGFR2,FLT1,FLT3,FLT4,KDR,KIT,PDGFRA,PDGFRB,RET*
Tafasitamab	*CD19*
Tagraxofusp	*CD123*
Talazoparib	*BRCA1,BRCA2*
Tamoxifen	*ESR1,ESR2*
Tazemetostat	*EZH2*
Temsirolimus	*MTOR*
Tepotinib	*MET*
Tisagenlecleucel	*CD19*
Tivozanib	*KDR,KIT,PDGFRB*
Toremifene	*ESR1*
Tositumomab	*MS4A1*
Trametinib	*MAP2K1,MAP2K2,BRAF*
Trastuzumab	*ERBB2*
Trastuzumab emtansine	*ERBB2*
Tretinoin	*RXRB,RXRG,RARG*
Trilaciclib	*CDK4,CDK6*
Tucatinib	*ERBB2*
Umbralisib	*PIK3CD,CSNK1E*
Vandetanib	*ABL1,EGFR,FLT1,FLT3,FLT4,KDR,RET,FGFR1*
Vemurafenib	*BRAF*
Venetoclax	*BCL2*
Vismodegib	*SMO*
Vorinostat	*HDAC1,HDAC2,HDAC3,HDAC6,HDAC8*
Zanubrutinib	*BTK,EGFR,ERBB2,ERBB4,ITK,BMX,JAK2,BLK,JAK3,PTK6,FRK,LCK*
Ziv-Aflibercept	*PGF,VEGFA,VEGFB*

2.3 Hypothesis and aim of the study

Targeted therapies are an increasingly important component of modern oncology, aiming at specific molecular alterations (e.g., receptors or proteins) that drive tumor growth. There are 155 drugs approved by FDA so far, which target different receptors and/or mostly proteins in cells(Daniel Alexander Hescheler et al., 2022). There are even more targeted agents in current clinical trials and due to this tremendous number of studies ongoing. Building on this concept and the previous study of Daniel A. Hescheler et al. (2020), this thesis tests the following hypotheses:

Hypothesis 1:

There are molecularly targeted agents currently under clinical investigation in non-gastric tumor entities that target oncogenic pathways and molecular alterations also present in gastric adenocarcinoma. Therefore, a subset of these agents represents potentially relevant therapeutic candidates for gastric cancer.

Hypothesis 2:

A detailed and systematic analysis of the clinical trial landscape, combined with an improved understanding of the molecular and molecular-pathologic basis of gastric adenocarcinoma (including recurrent pathways, biomarkers, and targetable alterations), enables the early identification and prioritization of such therapeutic candidates.

Accordingly, the aim of this work is to

(i) identify targeted therapies investigated in clinical trials,

(ii) assign their molecular targets, and

(iii) contextualize these targets within key oncogenic pathways relevant to gastric adenocarcinoma.

A similar study was executed by Hescheler et al. (Daniel A. Hescheler et al., 2020), which identified all already approved FDA targeted therapies and then cross-referenced their target genes with genomic alterations of 393 patients with gastric cancer. It identified two agents, which according to its in-silico analysis would expand treatment possibilities and target even a wider spectrum of gastric tumors then currently investigated according to the national guideline. These results must be confirmed in clinical trials but contribute to new insights in research of new treatment strategies for gastric cancer patients. A similar framework is used here, although this time targeted therapies in clinical trials must be identified at first not only for trials concerning gastric cancer, but as a wide range of cancer entities and trials as possible. This review is limited to the extent of targeted therapies in clinical trials being found, which due to the fast-changing nature of trials and the limited resources is not expected to report every single agent, but at least portray the landscape of targeted therapies nowadays and present an overview over new emerging options.

3 Materials und methods

3.1 Samples

This work has been online research only. Only information from databases and websites were obtained and no patients, samples or drugs were handled.

3.2 Databases

The acquisition of data was obtained only through databases and public accessible websites by mostly governmental and official authorities. The database and source of information are shortly introduced in the following paragraphs:

3.2.1 Clinicaltrials.gov

Clinicaltrials.gov is a website serviced by the U.S. National Library of Medicine(National Library of Medicine, 2022) and the U.S. National Institute of Health(National Institute of Health, 2022). It supplies health care professional as well as patients with information on clinical trials that have been registered. Details on trials are being provided by the principal investigator or the sponsor of a trial and should be regularly updated. Studies are not limited to the United States of America but include 220 countries. Information provided consists of a national clinical trial number (NCT), the disease or condition treated, the kind of intervention used (drugs, procedures, etc.), the requirements for participation like age, gender, and details to diseases progress, the locations of the trials and the title including a short description of the trials and an overview over the study design. Investigators are also able to publish results on this website since 2008. In the end of 2021 almost 400,000 studies were registered on clinicaltrials.gov with 52% in non-U.S. countries only(clinicaltrials.gov, 2022).

3.2.2 AdisInsight

AdisInsight is drug database from Springer Nature Switzerland, providing information on latest drug developments including clinical trials, adverse drug events reports and other information. Its content is constantly updated by staff and several sources are being provided. Contents are only available for paying subscribers. Drugs are being presented in profiles with information among others on drug properties, pharmacokinetics and -dynamics, and development status as well as history. Access was granted for one week from November 19th, 2020, until November 26th, 2020. During this time frame datasets were acquainted.

3.2.3 Drugbank online

Drugbank online(Wishart et al., 2018) is a free-of-charge database with information on drug compounds and their targets. It has pharmacological and pharmaceutical information as well as bioinformatics and cheminformatics assets combined in a profile. It is broadly used by different members in healthcare sector as well as in research. It is being updated regularly with

the last update (version 5.1.9), which was released on March 1st, 2022, containing 14,665 drugs of which 2,727 were small molecule therapies, 6,693 experimental compounds as well as antibody therapies and biologics(Drugbank Online, 2022).

3.2.4 Drug dictionary of National Cancer Institute

The National Cancer Institute is operated and funded by the federal U.S. government and responsible for cancer research and training within the United States. It supports 71 designated cancer centers and coordinates about 2,500 clinical trials. It also provides information in form of dictionaries on their website including the drug dictionary, which can be used to identify targets of targeted therapies and their mechanism of action. An entry contains general information about the composition of a drug and its main targets(The National Cancer Institute, 2022).

3.2.5 PubMed

PubMed is an open access database presenting literature and research on biomedical and life sciences. It includes more than 34 million citations and abstracts. Additionally, it provides links to publications and their official website as well as information about authors and journal(PubMed.gov, 2022). PubMed is operated by the National Center for Biotechnology Information(National Library of Medicine) at the U.S. National Library of Medicine(National Library of Medicine, 2022) and located at the National Institutes of Health(National Institute of Health, 2022).

3.2.6 KEGG

The Kyoto Encyclopedia of Genes and Genomes (KEGG) and the KEGG pathway database(Kanehisa Laboratories, 2022) contains a set of manually sketched diagrams about pathway interactions that are known so far. There are different types of maps and connections available as well as a list of all genes and proteins included in a pathway. KEGG in general is a database that combines genomic, chemical and systemic functional information. It was initiated with the purpose to create a better knowledge of interacting functions, systems and organisms after sequencing the genome(Kanehisa, 2000).

3.3 Software

For the analysis, as well as the production of tables, solely Microsoft® Word for Mac (Version 16.50) and Excel for Mac (Version 16.50) were used. No statistical or other analyses was executed. For the creation of Figure 13 the open access program ‘Cytoscape’ (Version 3.9.0)(Shannon et al., 2003) was used.

3.4 Methods

The flow diagram of the methodological proceed is shown in Figure 8 and displays on what criteria and by which sources targeted therapies in clinical trials and all additional information were identified.

3.4.1 Identification of clinical trials and targeted therapies

First of all, the search engines clinicaltrials.gov(Medicine, 2022) and AdisInsight(Switzerland Springer Nature, 2022) were screened for clinical trials. Searches were conducted as seen in Table 5.

Table 5 Search criteria for all sources in detail

1	Adis Insight	
	Selected options	‘targeted therapy’ ‘active status’ ‘cancer’ ‘all phases’
	results	1726 trials
2	Clinicaltrials.gov	
	search phrases	‘gene’ (implicated by clinical trials: ‘neoplasm’ and ‘tumor’, ‘cancer’ (implicated by clinical trials: ‘neoplasm’ and ‘tumor’),
	selected options	‘Interventional studies’; phases: ‘early phase I, I, II, III and/or IV’;
	start date	on or after 01/01/2015
	results	1600 trials
3	search phrases	‘mutation’ (implicated by clinical trials: ‘mutated’), ‘cancer’ (implicated by clinical trials: ‘neoplasm’ and ‘tumor’)
	selected options	‘Interventional studies’; phases: ‘early phase I, I, II, III and/or IV’;
	start date	on or after 01/01/2015
	results	1687 trials
4	search phrases	‘Targeted therapy’ (implicated by clinical trials: ‘treatment’ and ‘target’), ‘cancer’ (implicated by clinical trials: ‘neoplasm’ and ‘tumor’)
	selected options	‘Interventional studies’; phases: ‘early phase I, I, II, III and/or IV’;
	start date	on or after 01/01/2015
	results	3159 trials

For clinicaltrials.gov(Medicine, 2022) the following search phrases were used: ‘target(ed)’, ‘mutation/mutated’ and ‘gene’ plus the phrase ‘cancer’. Clinicaltrials.gov automatically includes similar phrases to ensure better search results. As synonyms for ‘cancer’, ‘tumor’ and

‘neoplasm’ were added. The database also included ‘mutated’ to ‘mutation’ and ‘treatment’ and ‘target’ for the phrase ‘targeted therapy’. No additional search terms were applied beyond this predefined keyword set, to maximize sensitivity and avoid missing relevant records.

All queried databases provided exportable spreadsheets listing the retrieved clinical trials and/or drug records and their molecular targets (Switzerland Springer Nature, 2022). Trial duplicates were excluded as well as trials not related to cancer. The lists of clinical trials contained information like, interventions/drugs used, study type, clinical phase, start date as well as the NCT numbers. Only trials or targeted therapies that had been started after the 1st of January 2015 were included to ensure that no totally outdated treatments were included. For each clinical trial all employed drugs and each therapy were checked in the database of DrugBank(Switzerland Springer Nature, 2022), if it was a targeted therapy and of it was already approved by the FDA for any indication, not only gastric adenocarcinoma. The next step was to check their target gene or protein in the drug dictionary of the National Cancer Institute (NCI)(The National Cancer Institute, 2022) for their target mechanism and if it was applicable in cancer research. If all these conditions applied the targeted therapy was added to the list of targeted therapies in clinical trials. Vaccines as well as immunotherapies like CAR T-cell treatments were not included as these weren’t intended on by the search phrases and could have given a wrong impression of these therapies.

For the purposes of this thesis and as the previous study had already focused on FDA approved drugs by Daniel A. Hescheler et al. (2020), agents with existing FDA approval were excluded from the investigational set to focus on emerging therapies. Nevertheless, FDA-approved agents for other cancer entities may still be discussed in the work where they illustrate repurposing potential or mechanistic relevance to gastric adenocarcinoma. Furthermore, the lists of trials and information overall was gathered between November 1st, 2020, and March 31st, 2021, and any therapies that have been approved since this period may still show or may be marked as not FDA-approved. Evaluation of data and checking for FDA approval for any indication was completed between November 1st, 2020, and January 30th, 2022.

Because the initial screening was not restricted to gastric cancer alone, basket and umbrella trials recruiting multiple tumor entities (including gastric or gastroesophageal adenocarcinoma) were captured where they met the inclusion criteria.

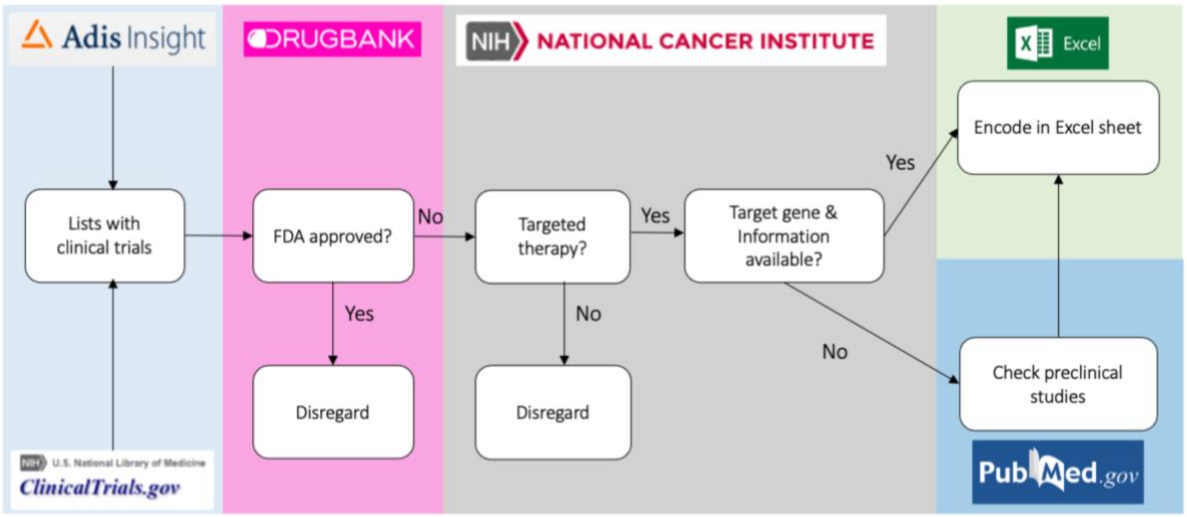


Figure 8 Flow diagram of methodological proceed.

3.4.2 Target therapy inclusion criteria

There is no exact universal definition for targeted therapies, but in chapter 2.2 targeted therapies four main principles of a definition were identified. These characteristics set the idea for inclusion criteria:

- A well-defined target or biological pathway that constitute a certain kind of cancer,
- a target that is measurable in a clinical setting to identify patients who benefit from treatment as well as monitor progress (availability of biomarkers),
- minimal damage to non-cancer cells and thereby a high specificity to malignant cells,
- treatment is restricting growth, differentiation or proliferation of cancer cells or their environment.

The cutoff criteria to which an agent or a therapy was still considered a targeted therapy was set with a wide range to include as many therapies as possible. In general, a targeted therapy is an agent which has a well-defined target or biological pathway that drives the cancer phenotype or its natural environment(Sledge, 2005). It also must be measurable in a clinical setting, so suitable patients can be identified and included to treatment on the expression of certain molecular markers(Joo, Visintin, & Mor, 2013). As a third inclusion criteria it should be able to identify cancer cells or a tumor environment and cause normal cells only minimal harm (Mendelsohn et al., 2014). If a drug or treatment option was indecisive it was rather included than eliminated from the list of targeted therapies in clinical trials.

3.4.3 Identifying all clinical trials concerning one targeted therapy

After all clinical trials have been examined, the resulting list of targeted therapies in clinical trials was once more investigated, each targeted therapy independently in clinicaltrials.gov(Medicine, 2022), to identify all studies ongoing concerning each compound. The name of each targeted therapy was put in the search phrases of clinicaltrials.gov.

Afterwards all clinical trials were counted individually by phases and their according status. Therefore the preset classification of status and study phase(s) was adopted from clinicaltrials.gov(Medicine, 2022), namely: ‘recruiting’, ’not-yet recruiting’, Active, not recruiting’, ‘completed’, ‘unknown’, ‘terminated’, ‘withdrawn’, and ‘suspended’ and the phases ‘phase I’, ‘phase II’, ‘phase III’, and ‘phase IV’. Phases ‘early I’ and ‘I’ were merged into the category ‘phase I’. If one trial included two phases, for example ‘phase I’ and ‘phase II’, it was defined as ‘phase I/II’. And if there were various clinical trials for one targeted therapy in different clinical phases the lowest phase related to the highest phase, for example ‘phase I-III’. If a compound was just investigated in two different clinical trials which were in different phases, it was linked with an ‘&’, for example ‘phase I&II’.

4 Results

In total 8214 trials and 16460 therapies have been investigated each independently over the period of ten months from January 2021 until October 2021. In total 8214 clinical trials with 16460 therapies were identified, with 6446 (14692 therapies) trials on clinicaltrials.gov(Medicine, 2022) and 1768 trials (1768 therapies) on AdisInsight(Switzerland Springer Nature, 2022). In a first step 6388 duplicated therapies and 1656 duplicates in clinical trials were excluded and 356 trials as well as 689 therapies were not related to cancer and therefore eliminated.

According to that, 6202 trials and 9383 therapeutics were investigated. In the following process, therapies were excluded if they weren't falling under the definition of a 'targeted therapy' (8496 drugs), have already been approved by the FDA (155 targeted therapies), or were defined as CAR-T-Cells (45 treatment options) or cancer vaccines (23 therapies). At last, a total of 2433 clinical trials were included identifying 905 targeted therapies and 320 target genes (Figure 9).

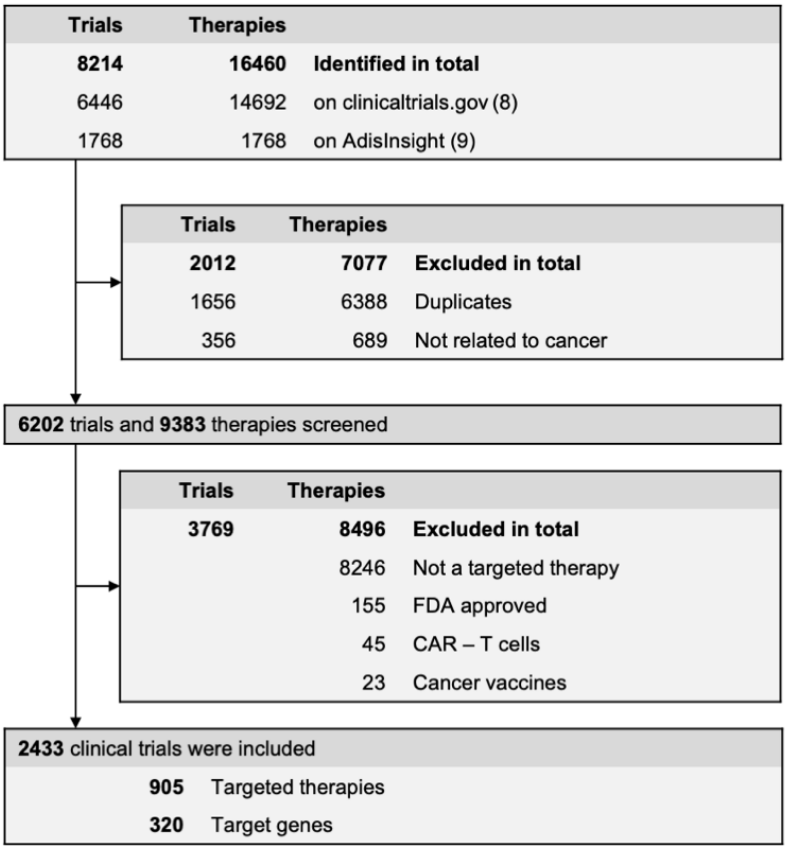


Figure 9 Process of identifying targeted therapies

4.1 Clinical trials distributions

In total 905 targeted therapies in clinical trials that are not yet FDA-approved were identified with respectively 2433 clinical trials. In a second investigation all clinical trials were identified

that included the recognized 905 targeted therapies. The clinical studies can be subdivided in their clinical phases from I to IV as or according to their current status, which can range from ‘active recruiting’ to ‘withdrawn’ or ‘completed’.

4.1.1 Study phases

There were 7,940 clinical trials identified in total. Their distribution regarding the different clinical phases is shown in Figure 10 and were conducted as described in the methodological approach. There are 2614 clinical trials in phase I. Most of the trials were in phase II (3134 trials). 1199 trials were in both phase I and II, therefore marked here as a separate ‘phase I/II’. A total of 568 clinical trials were in phase III. 151 studies were run in both phases II and III and therefore categorized as ‘phase II/III’. Additionally, 64 trials in phase IV were identified.

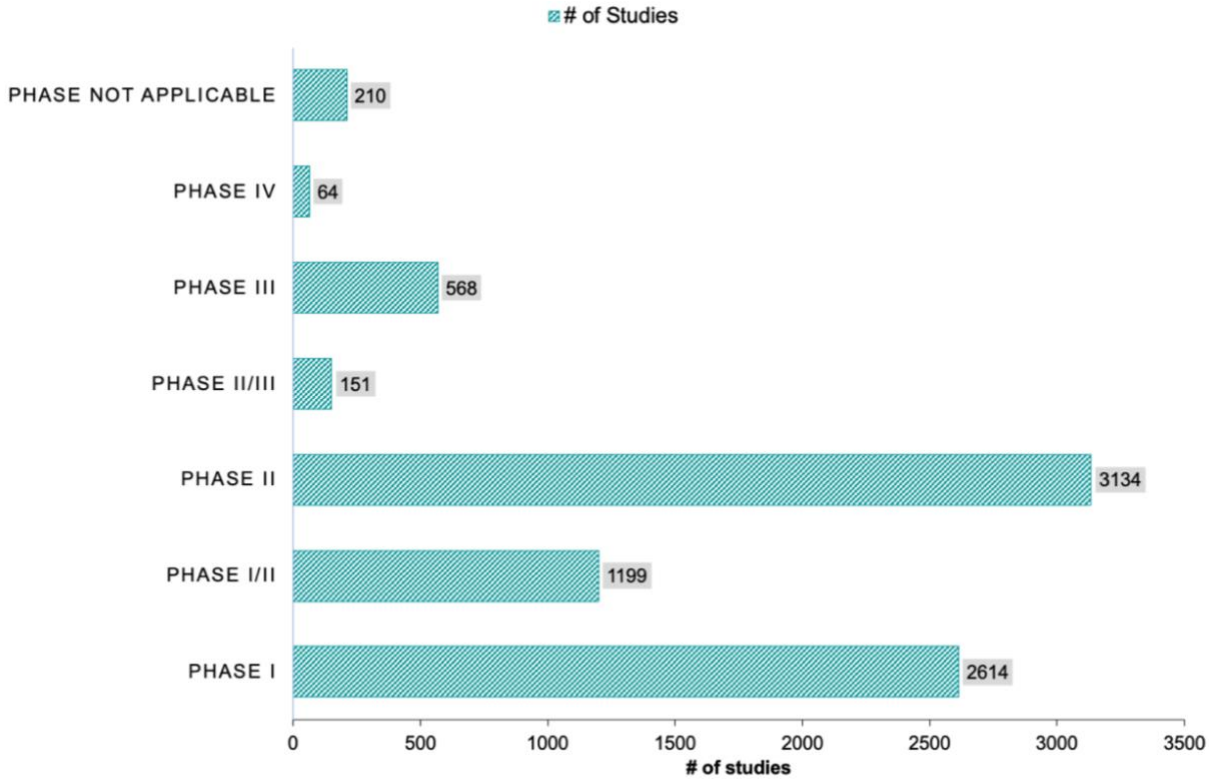


Figure 10 Distribution of clinical trials in different clinical phases

However not only the trials can be characterized according to their phases. The 905 targeted therapies were designated into groups according to their range of clinical phases due to their stages they have been ongoing between 01.01.2015 and 01.10.2021. Most of the targeted therapies are in phase I and II (322). 314 are just in the start of clinical trials in phase I, 158 displayed trials in phases I-III and 89 were just in phase I/II trials. 17 were already at the phase I-IV. There were also 13 drugs, which were just in phase II and 2 just in phase III since 01/01/2015.

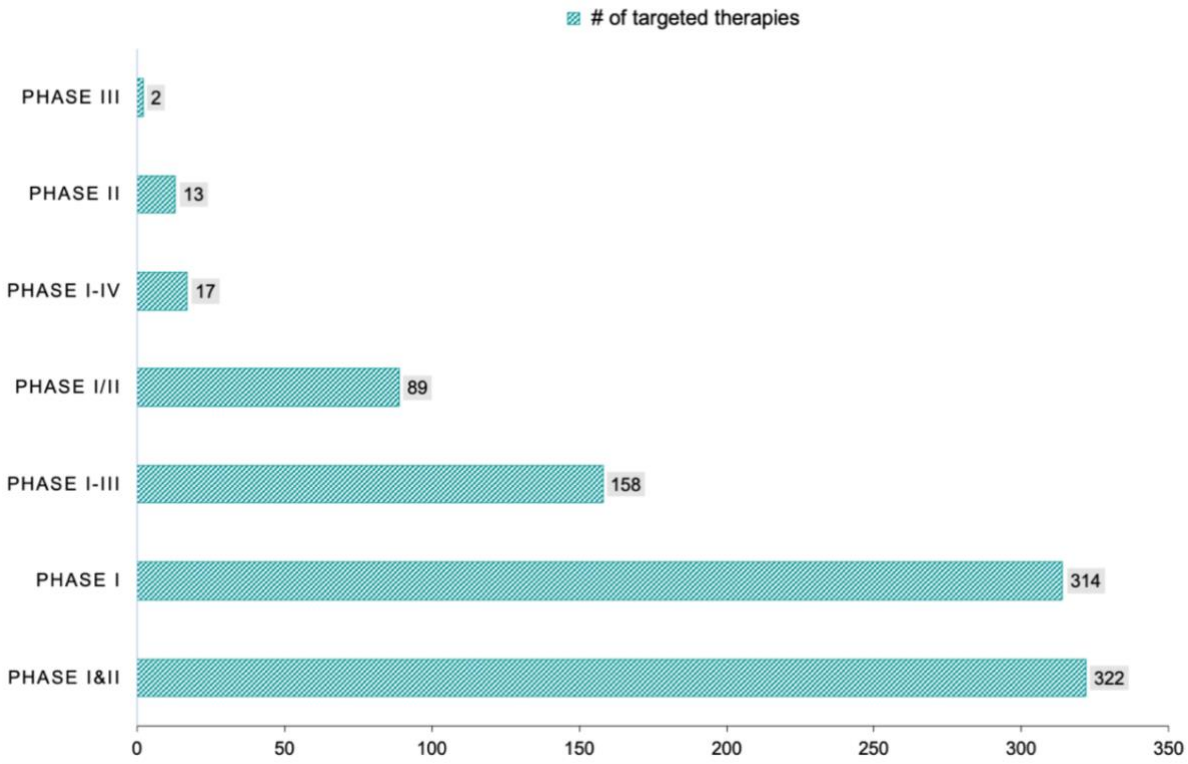


Figure 11 Number of targeted therapies and their current clinical phases

4.1.2 Different status

The clinical trials can also be assigned into groups corresponding to their current status. Most of the clinical trials since 01/01/2015, 2776, are still recruiting and 2108 were completed since the first of January 2015. 917 trials have not yet started recruiting, 831 are ‘active, not recruiting’, 569 ‘unknown’, 521 ‘terminated’, 230 ‘withdrawn’ and 35 ‘suspended’. These

statuses were identified between 01/10/2021 and 15/10/2021. Statuses have probably changed since the last update.

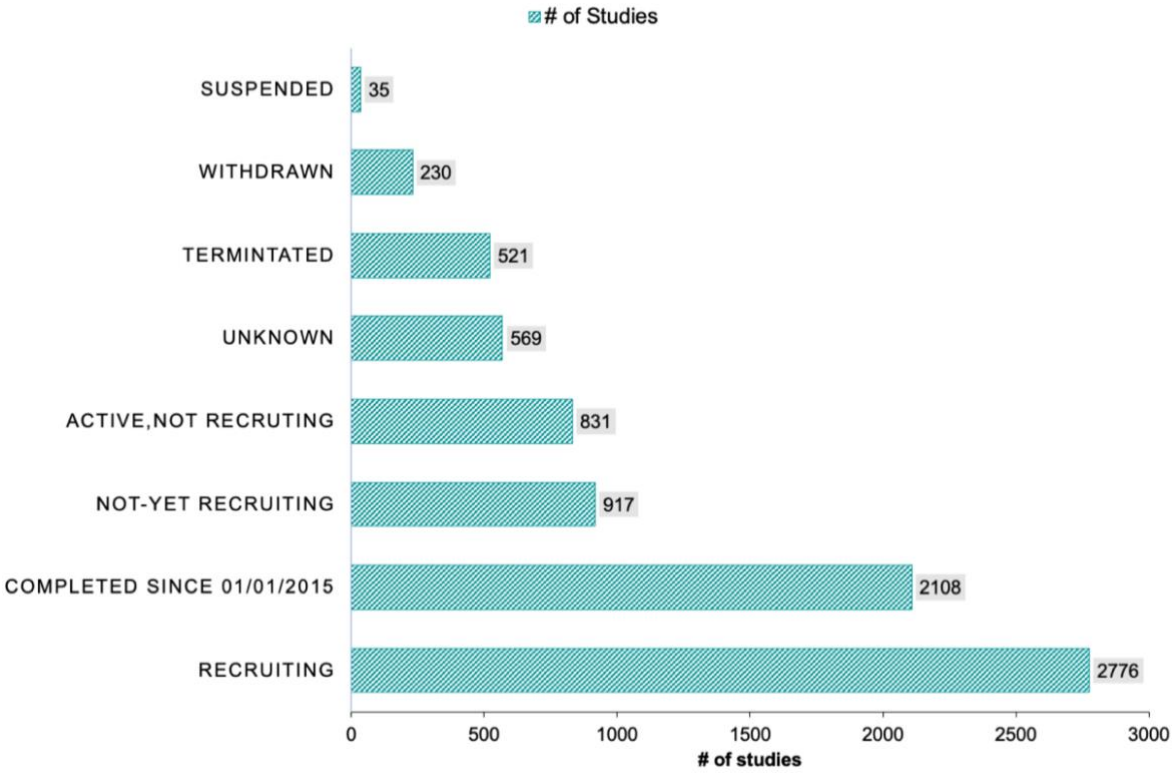


Figure 12 Distribution of clinical trials in every different status

4.1.3 List of all targeted therapies in clinical trials

In total a sum of 905 targeted therapies were identified targeting 320 different target genes or proteins that were marked according to their characteristic gene. Table 6 shows all identified targeted therapies in alphabetical order including their target genes and the range of phases their clinical trials were in.

Table 6 List of all identified targeted therapies, their regarding target genes and their clinical phases.

Drug	Gene Targets	Clinical Phases
(211-AT)OKT10-[131I]-SGMIB	CD38 ERBB2	Phase I Phase I&II
2X-121*	PARP1,PARP2,TNKS1,TNKS2	Phase II
9-ING-41*	GSK3A	Phase I&II
A166*	ERBB2	Phase II-IV
AB680*	NT5E	Phase I&II
ABBV-321*	EGFR	Phase I
ABBV-CLS-484*	PTPN2	Phase I
Abivertinib*	EGFR, BTK	Phase I-III
ABL503*	TNFRSF9	Phase I
ABM1310*	BRAF	Phase I
ABN401*	MET	Phase I/II
ABT-414*	EGFR	Phase I-III
ACE 1702*	ERBB2	Phase I
Adagrasib*	KRAS	Phase I&II
Adavosertib*	WEE1,CDK1,CDK2	Phase I&II
ADCT-602*	CD22	Phase I/II
Adebrelimab*	CD274	Phase I-III
ADG 106*	TNFRSF9	Phase I&II
AEE788*	EGFR,KDR,ERBB2	Phase I&II
AFM 24*	EGFR	Phase I/II
AFM13*	CD30	Phase I&II
afuresertib*	AKT1,AKT2,AKT3	Phase I&II
AG-270*	MAT2A	Phase I
AGEN2034*	PDCD1	Phase I-III
agerafenib*	EGFR	Phase I&II
AGS-16C3F*	ENPP3	discontinue
AK104*	PDCD1,CTLA4	Phase I-III
AK-109*	KDR	Phase I&II
AK112*	PDCD1,KDR,FLT1,FLT4	Phase I&II
AK117*	CD47	Phase I&II
AK119*	NT5E	Phase I
AL101*	NOTCH1,NOTCH2,NOTCH3,NO	Phase I-III
AL2846*	MET	Phase I&II
alflutinib	EGFR	Phase I-III
Alisertib*	AURKA	Phase I-III
ALLO 501*	CD19	Phase I&II
ALLO 715*	TNFRSF17	Phase I
ALLO-316*	CD70	Phase I
Almonertinib*	EGFR	Phase I-III
ALN-VSP*	KDR,FLT1,FLT4	Phase I
ALRN-6924*	MDM2	Phase I&II
Alsevalimab*	VTCN1	Phase I&II
ALT-P7*	ERBB2	Phase I
ALX 148*	CD47	Phase I-III
AMB-05X*	CSF1R	Phase II
AMC303*	CD44	Phase I
Amcenestrant*	ESR1	Phase I-III
AMG 160*	FOLH1	Phase I&II
AMG 232*	MDM2	Phase I-III
AMG 337*	MET	Phase I&II
AMG 404*	PDCD1	Phase I&II
AMG 420*	TNFRSF17	Phase I-III
AMG 562*	CD19	Phase I
AMG 595*	EGFR	Phase I
AMG 650*	KIF18A	Phase I
AMG 757*	DLL3	Phase I&II
AMG337*	MET	Phase I&II
AMG-650*	ESR1	Phase I
AMXI-5001*	PARP1,PARP2	Phase I/II
AN4005*	CD274	Phase I
anbenitamab*	ERBB2	Phase I&II
Andecaliximab*	MMP9	Phase I-III
Anetumab	MSLN	Phase I&II
ANG1005*	LRP1	Phase III
AO-176*	CD47	Phase I/II
Apatinib *	KDR,FLT1,FLT4	Phase I-IV
APG 115*	MDM2	Phase I&II
APG 1387*	XIAP	Phase I&II
APG 2449*	ALK,PTK2,ROS1	Phase I
APG-115*	TP53,MDM2	Phase I&II
APG-2575*	BCL2	Phase I&II
APL-101*	MET	Phase I&II
APL-1202*	METAP2	Phase I-III
APN-431*	CBLB	no
APTO 253*	MTF1	Phase I
APVO 436*	IL3RA	Phase I
APX 3330*	APEX1	Phase I&II
APX005M*	CD40	Phase I&II
Archexin*	AKT1	Phase I&II
ARO HIF2*	EPAS1	Phase I
ARQ 531*	BTK	Phase I&II
ARQ751*	AKT1,AKT2,AKT3	Phase I
ARRY 461*	CD47	Phase I
ARRY-382*	CSF1R	Phase I&II
ARV 110*	AR	Phase I/II
ARV-471*	ESR1	Phase I/II
ARX517*	FOLH1	Phase I
ARX788*	ERBB2	Phase I&II
asciminib*	DLL4,KDR	Phase I-III
ASN003*	BRAF,PTEN,PIK3CA	Phase I
ASP1650*	CLDN6	Phase II
ASTX029*	MAPK1,MAPK3	Phase I&II
ASTX295*	MDM2	Phase I/II
AT7519*	CDK1,CDK2,CDK4,CDK5,CDK6,C	Phase I&II
Atamparib*	TIPARP	Phase I
ATG 019*	PAK4,NAMPT	Phase I
ATG-101*	CD274	Phase I
AV 203*	ERBB3	Phase I
avitinib maleate*	EGFR	Phase I-III
axatilimab*	CSF1R	Phase I&II
AZD0466*	BCL2,BCL2L1	Phase I&II
AZD1390*	ATM	Phase I
AZD1480*	JAK2	Phase I
AZD4205*	JAK1	Phase I&II
AZD4547*	FGFR1,FGFR2,FGFR3	Phase I-III
AZD4573*	CDK9	Phase I
AZD4785*	KRAS	Phase I
AZD5153*	BRD4	Phase I&II
AZD-5305*	PARP1,PARP2	Phase I/II
AZD5991*	MCL1	Phase I
AZD8186*	PIK3CB	Phase I&II
AZD9496*	ESR1	Phase I
AZD9833*	ESR1	Phase I-III
BA 3011*	AXL	Phase I&II
balixafortide*	CXCR4	Phase I-III
barasertib*	AURKB	Phase I-III

Drug	Gene Targets	Clinical Phases
Barecetamab*	ERBB3	Phase I
BAT 8001*	ERBB2	Phase I-III
Batiraxcept*	AXL	Phase I-III
BAY1143269*	EIF4E	Phase I
BAY1251152*	CDK9	Phase I
BAY1436032*	IDH1	Phase I
BAY1862864*	CD22	Phase I
BAY2315497*	FOLH1	Phase I
BAY2701438*	ERBB2	Phase I
BAY2701439*	ERBB2	Phase I
BAY2701439*	ERBB2	Phase I
BBP398*	PTPN11	Phase I
BBT-176*	EGFR	Phase I/II
BCA101*	EGFR,TGFB1	Phase I
BCD-115*	CDK8,CDK19	Phase I
BCD-147*	ERBB2	Phase I
BDC 1001*	ERBB2	Phase I/II
BDTX-189*	EGFR,ERBB2	Phase I/II
Belvarafenib*	BRAF,NRAS,KRAS,RAF1	Phase I&II
Bemarituzumab*	FGFR2	Phase I&II
Bemcentinib*	AXL	Phase I&II
Bermekimab*	IL1A	Phase I-III
Berzosertib*	ATR	Phase I&II
BGB-10188 *	PIK3CD	Phase I/II
BGB-16673*	BTK	Phase I
BGB3245*	BRAF	Phase I
BGB-3245*	BRAF	Phase I&II
BHQ-880 *	DKK1	Phase I&II
BI 1701963*	KRAS,SOS1	Phase I
BI 1810631*	ERBB2	Phase I
BI 1823911*	KRAS	Phase I
BI 3011441*	MAP2K1	Phase I
BI 754091*	PDCD1	Phase I&II
BI 836826*	CD37	Phase I&II
BI 836858*	CD33	Phase I&II
BI 853520*	PTK2	Phase I
BI 894999*	BET	Phase I
BI 905711*	CDH17	Phase I
BI 907828*	TP53,MDM2	Phase I
BI-754091*	PDCD1	Phase I&II
BIIB091*	BTK	Phase I
Bimiralisib*	PIK3CA,PIK3CB,PIK3CD,PIK3CG,	Phase I&II
bintrafusp alfa*	PDCD1	Phase I-III
BION-1301*	TNFRSF13B,TNFRSF17	Phase I&II
Birabresib*	BRD2,BRD3,BRD4	Phase I&II
BJ 001*	ITGB3,ITGB5,ITGB6	Phase I
BL-8040*	CXCR4	Phase I-III
BLU-945*	EGFR	Phase I/II
BLZ945*	CSF1R	Phase I&II
BMS-599626*	EGFR,ERBB2,ERBB3,ERBB4	Phase I
BMS-690514*	EGFR,ERBB2,ERBB4,FLT1,FLT4,	Phase I&II
BMS-813160*	CCR2,CCR5	Phase I&II
BMS-986004*	CD40	Phase I/II
BMS-986148*	MSLN	Phase I&II
BMS-986158*	BRD2,BRD3,BRD4,BRDT	Phase I&II
BMS-986179*	NT5E	Phase I/II
BOS172738*	RET	Phase I
Bozitinib*	MET	Phase I&II
BPI-1178*	CDK4,CDK6	Phase I/II

Drug	Gene Targets	Clinical Phases
BPI15086*	EGFR	Phase I
BPI-15086*	EGFR	Phase I
BPI-9016M*	AXL,MET	Phase I
BPX-601*	PSCA	Phase I&II
BPX-701*	PRAME	Phase I/II
Briciclib*	CCND1	Phase I
Brilanestrant*	ESR1	Phase I
budigalimab*	PDCD1	Phase I&II
Buparlisib*	PIK3CA,PIK3CB,PIK3CD,PIK3CG	Phase I-III
burixafor*	CXCR4	Phase I&II
Burosumab*	FGF23	Phase I-III
BZ019*	CD19	Phase I
CA 4948*	IRAK4,FLT3	Phase I/II
CA-170*	CD274,PDCD1LG2,VSIR	Phase I&II
CA-4948*	IRAK4	Phase I/II
cabiralizumab*	CSF1R	Phase I&II
Camidanlumab	IL2RA	Phase I&II
Camrelizumab*	PDCD1	Phase I-III
CAN008*	FAS	Phase I&II
capivasertib*	AKT1,AKT2,AKT3	Phase I&II
carotuximab*	ENG	Phase I-III
Catequentinib*	FGFR1,FGFR2,FGFR3,FGFR4,KIT	Phase I-IV
Catumaxomab*	EPCAM	Phase I-III
CB-010*	CD19	Phase I&II
CB-03-10*	NR3C1,AR	Phase I
CB-103*	NOTCH1,NOTCH2,NOTCH3,NO	Phase I/II
CB307*	FOLH1	Phase I
CC 90010*	BRD2,BRD3,BRD4,BRDT	Phase I&II
CC 97540*	CD19	Phase I
CC 98633*	TNFRSF17	Phase I
CC-90002*	CD47	Phase I
CC-90003*	MAPK1	Phase I
CC-90011*	KDM1A	Phase I&II
CC-98633*	TNFRSF17	Phase I
CCS1477*	EP300	Phase I/II
CCT303-406*	ERBB2	Phase I
CDX-1140*	CD40	Phase I&II
CDX-301*	FLT3	Phase I&II
CDX-3379*	ERBB3	Phase I&II
CDX-527*	CD274	Phase I
Cediranib*	KDR,FLT1,FLT4	Phase I-III
CEP-11981*	TEK,KDR,FLT1,FLT4	Phase I&II
Ceralasertib*	ATR	Phase I&II
Cerdulatinib*	SYK,JAK1,JAK3	Phase I-III
Cergutuzumab	CEACAM5	Phase I
cetrelimab*	PDCD1	Phase I-III
CFI 402257*	TTK	Phase I&II
CFI-400945*	PLK4	Phase I&II
CFI-402257*	TTK	Phase I&II
CG-806*	FLT3,BTK	Phase I
CHC2014*	NTRK1,NTRK2,NTRK3	Phase I
Chiauranib*	KIT,KDR,PDGFR,AURKB,FLT1,FL	Phase I-III
CHO-H01*	MS4A1	Phase I
cibisatamab*	CEACAM5	Phase I&II
CID-103*	CD38	Phase I
cinrebafusp alfa*	ERBB2	Phase I
Cirmtuzumab*	ROR1	Phase I&II
Cirtuvivint*	WNT1	Phase I
CKD-702*	EGFR,MET	Phase I

Drug	Gene Targets	Clinical Phases
CLIC-1901*	CD19	Phase I/II
CLN-081*	EGFR	Phase I/II
CM313*	CD38	Phase I
CM93*	EGFR,EGFRVIII	Phase I
CMB305*	CTAG1B	Phase I&II
Cofetuzumab	PTK7	Phase I
Cosibelimab*	PDCD1	Phase I-III
COTI 2*	TP53,AKT1,AKT2,AKT3	Phase I
CPGJ602*	EGFR	Phase I&II
CPI-006*	NT5E	Phase I-III
CPI-1205*	EZH2	Phase I&II
CPI-818*	ITK	Phase I
CPL304110*	FGFR1,FGFR2,FGFR3,FGFR4	Phase I
CPO107*	MS4A1,CD47	Phase I/II
crenigacestat*	NOTCH1,NOTCH2,NOTCH2,NO	Phase I&II
Crenolanib*	PDGFRA,PDGFRB,FLT3	Phase I-III
CT 0508*	ERBB2	Phase I-IV
CT041*	CLDN18	Phase I&II
CT053*	TNFRSF17	Phase I&II
CT7001*	CDK7	Phase I/II
CTT1057*	FOLH1	Phase I-III
CTT1403*	FOLH1	Phase I
CTX 130*	CD70	Phase I-IV
CX-2009*	ALCAM	Phase I&II
CYH33*	PIK3CA	Phase I&II
CYT-0851*	RAD51	Phase I/II
D-0316*	EGFR	Phase I-III
D-0502*	ESR1	Phase I
D-1553*	KRAS	Phase I/II
Dactolisib*	PIK3CA,PIK3CD,PIK3CG,MTOR	Phase I-III
Dalpiciclib*	CDK4,CDK6	Phase I-III
Danusertib*	AURKB,AURKA,AURKC	Phase II
Danvatirsen*	STAT3	Phase I&II
Darovasertib*	PRKCA,PRKCQ,GSK3B	Phase I&II
datopotamab	TACSTD2	Phase I-III
DBPR112*	EGFR	Phase I
DCC-3116*	ULK1,ULK2	Phase I
DCLL9718S*	CLEC12A	Phase I
DCR-MYC*	MYC	Phase I
Defactinib*	PTK2	Phase I&II
Depatuxizumab*	EGFR	Phase I-III
derazantinib*	FGFR1,FGFR2,FGFR3	Phase I&II
DF1001*	PDCD1	Phase I/II
DFF332*	EPAS1	Phase I
DHES0815A*	ERBB2	Phase I
Disitamab	ERBB2	Phase I-III
Divozilimab*	MS4A1	Phase I&II
DKN-01*	DKK1	Phase I&II
domatinostat*	HDAC1,HDAC2,HDAC3,BRD4	Phase I&II
dovitinib*	KIT,PDGFRA,FLT3,KDR,FGFR3,F	Phase I-III
DP303c*	ERBB2	Phase I
DS 1055a*	LRRC32	Phase I
DS-1001*	IDH1	Phase I&II
DSP107*	CD47	Phase I&II
DSP-7888*	WT1	Phase I-III
DT2216*	BCL2L1	Phase I
DT2219ARL*	CD19,CD22	Phase I&II
DTRM-555*	MTOR,BTK	Phase I&II
Dubermatinib*	AXL	Phase I&II

Drug	Gene Targets	Clinical Phases
DZD9008*	EGFR	Phase I&II
E 6201*	MAP2K1,MAP3K1	Phase I&II
E7090*	FGFR1,FGFR2,FGFR3	Phase I&II
EC 0652*	FOLH1	Phase I
EC1169*	FOLH1	Phase I
Eganelisib*	PIK3CG	Phase I&II
Elimusertib*	ATR	Phase I
Elranatamab*	TNFRSF17	Phase I-III
eltanexor*	XPO1	Phase I/II
EMB-01*	MET,EGFR	Phase I-III
Enoblituzumab*	CD276	Phase I-III
Ensartinib*	ALK	Phase I-III
Entospletinib*	SYK	Phase I-III
Envafolimab*	PDCD1	Phase I-III
enzastaurin*	PIK3CA,PRKCB,AKT1,AKT2,AKT	Phase I-III
EP-100 *	GNRH1	Phase I&II
Epacadostat*	IDO1	Phase I-III
epitinib*	EGFR	Phase I
Epratuzumab*	CD22	Phase I-III
Eprenetapopt*	p53	Phase I-III
ERAS-007*	MAPK3,MAPK1	Phase I/II
ERY974*	GPC3	Phase I
ESG401*	TACSTD2	Phase I&II
ETH-155008*	FLT3,CDK4,CDK6	Phase I
Fadraciclib*	CDK2,CDK9,CDK5	Phase I&II
Famitinib*	KIT,PDGFR,FLT4,FLT3,KDR	Phase I-III
Farletuzumab*	FOLR1	Phase I&II
FAZ053*	CD274	Phase I
FCN-011*	NTRK1,NTRK2,NTRK3	Phase I
FCN159*	MAP2K1,MAP3K1	Phase I&II
FCN411*	EGFR,ERBB2	Phase I/II
FCN-437*	CDK4,CDK6	Phase I&II
Felezonexor*	XPO1	Phase I
FF-10101-01*	FLT3	Phase I/II
FHD-286*	SMARCA4, SMARCA2	Phase I
FHD-609*	BRD9	Phase I
Fibromun*	FN1	Phase I&II
Ficlatuzumab*	MET	Phase I&II
Fimepinostat*	PIK3CA,PIK3CB,PIK3CD,HDAC1	Phase I&II
Fisogatinib*	FGFR4,FGF19	Phase I&II
Flotetuzumab*	IL3RA	Phase I&II
Flumatinib*	PDGFR,KIT	Phase I-IV
Fluzoparib*	PARP1,PARP2	Phase I-III
FOR46*	CD46	Phase I-IV
Foritinib	ALK,ROS1	Phase I/II
FPX 01*	IGF1R	Phase I
fruquintinib*	KDR,FLT1,FLT4	Phase I-IV
FS118*	CD274	Phase I/II
FS-1502*	ERBB2	Phase I
FS222*	PDCD1	Phase I
FT 596*	CD19	Phase I
FT 7051*	CREBBP,EP300,AR	Phase I
FT-1101*	BRD2,BRD3,BRD4,BRDT	Phase I
Futibatinib*	FGFR1,FGFR2,FGFR3,FGFR4	Phase I-III
Futuximab/modo	EGFR	Phase I-III
G1T48*	ESR1	Phase I
Galunisertib*	TGFBR1	Phase I-III
GC022F *	CD19,CD22	Phase I&II
GC1118*	EGFR	Phase I&II

Drug	Gene Targets	Clinical Phases
GDC-0919*	IDO1	Phase I
GDC-0927*	ESR1	Phase I
GDC-6036*	KRAS	Phase I
Gedatolisib*	PIK3CA,PIK3CD,PIK3CG,PIK3CB,	Phase I&II
GEM333*	CD33	Phase I
GEM-3-PSCA*	PSCA	Phase I
GEN1044*	TPBG	Phase I&II
GEN1046*	PDCD1	Phase I&II
genolimzumab*	PDCD1	Phase I&II
Giredestrant*	ESR1	Phase I-III
glembatumumab	GPNMB	Phase I&II
glofitamab*	MS4A1	Phase I-III
Glumetinib*	MET	Phase I&II
GNR-084*	CD19	Phase I/II
GQ 1001*	ERBB2	Phase I
GS-3583*	FLT3	Phase I
GSK2141795*	AKT1,AKT2,AKT3	Phase I&II
GSK2256098*	PTK2	Phase I&II
GSK2636771*	PIK3CB	Phase I&II
GSK2636771*	PIK3CB	Phase I&II
GSK2849330*	ERBB3	Phase I
GSK3145095*	RIPK1	Phase II
GSK3368715*	PRMT1	Phase I
GST-HG161*	MET	Phase I
GT90001*	ALK1	Phase I/II
Gusacitinib*	JAK1,JAK2,JAK3,TYK2,SYK	Phase I&II
H3B-6527*	FGFR4	Phase I
H3B-6545*	ESR1	Phase I&II
HB0025*	CD274	Phase I
HEC 68498*	MTOR,PIK3CA,PIK3CB,PIK3CG,	Phase I
HH2710*	MAPK3,MAPK1	Phase I/II
HL-085*	MAP3K1,RAF1	Phase I&II
HLX 208*	BRAF	Phase I&II
HLX20*	CD274	Phase I
HLX22*	ERBB2	Phase I&II
HLX23*	NT5E	Phase I
HLX55*	MET	Phase I
HM95573*	BRAF,RAF1	Phase I
HMPL306*	IDH1,IDH2	Phase I
HMPL-453*	FGFR1,FGFR2,FGFR3	Phase I&II
HMPL-523*	SYK	Phase I-III
HPN328*	DLL3	Phase I/II
HPN536*	MSLN	Phase I/II
HS 10241*	MET	Phase I&II
HS-10342*	CDK4,CDK6	Phase I&II
HS-10352*	PIK3CA	Phase I
HS269*	RET	Phase I
HWH340*	PARP1,PARP2	Phase I
HX008*	PDCD1	Phase I-III
I-131-	PTPRC	Phase I
IAH0968*	ERBB2	Phase I/II
Ianalumab*	TNFSF13B	Phase I-III
IBI315*	PDCD1,ERBB2	Phase I
IBI318*	CD274	Phase I&II
IBI322*	CD274	Phase I
IBI323*	CD274	Phase I
Icotinib*	EGFR	Phase I-IV
ICP-192*	FGFR1,FGFR2,FGFR3,FGFR4	Phase I&II
Idasanutlin*	MDM2	Phase I-III

Drug	Gene Targets	Clinical Phases
IDE397*	MAT2A	Phase I
IDH305*	IDH1	Phase I&II
Idronoxil*	ENOX2	Phase I-III
IDX-1197*	PARP1,PARP2	Phase I&II
Ifabotuzumab*	EPHA3	Phase I&II
IGM 2323*	MS4A1	Phase I
IGM-8444 *	TNFRSF10B	Phase I
Ilorasertib*	PDGFRA,PDGFRB,PDGFC,PDGF	Phase I&II
Imalumab*	MIF	Phase I&II
Imaradenant*	ADORA2A	Phase I&II
IMC CS4*	CSFR1	Phase I
IMC001*	CD274	Phase I&II
IMC002*	CD47	Phase I
IMC-3C5*	FLT4	Phase I
IMGN632*	IL3RA	Phase I/II
IMGN779*	CD33	Phase I
IMM0306*	MS4A1,CD47	Phase I
IMP4297*	PARP1,PARP2	Phase I-III
IMP7068*	WEE1	Phase I
IMP-7068*		
Inavolisib*	PIK3CA,PIK3CB,PIK3CD,PIK3CG	Phase I-III
INBRX-105*	TNFRSF9,PDCD1	Phase I&II
INCB057643*	BRD2,BRD3,BRD4,BRDT	Phase I&II
INCB059872*	KDM1A	Phase I&II
INCB062079*	FGFR4	Phase I
INCB086550*	CD274	Phase I&II
INCB099280*	CD274	Phase I
INCB099318*	PDCD1	Phase I
INCB7839*	ADAM10,ADAM17	Phase I&II
Indatuximab	SDC1	Phase I&II
INO5401*	WT1,FOLH1,TERT	Phase I&II
Ipatasertib*	AKT1	Phase I-III
IRX4204*	RXRA	Phase I&II
ISB 1342*	CD38	Phase I
Itacitinib*	JAK1	Phase I-III
JAB-21822*	KRAS G12C	Phase I/II
JAB-3068*	PTPN11	Phase I&II
JAB-3312*	KRAS	Phase I&II
JDQ443*	KRAS G12C	Phase I/II
JMT101*	EGFR	Phase I
JNJ-40346527*	CSF1R	Phase I&II
JNJ-67571244*	CD33	Phase I
JNJ-67856633*	MALT1	Phase I
JNJ-74699157*	KRAS	Phase I
JNJ-75229414*	KLK2	Phase I
JNJ-75276617*	KMT2A	Phase I
JNJ-75348780*	CD22	Phase I
JNJ-78278343*	KLK2	Phase I
JPI-547*	PARP1,PARP2,TNKS1,TNKS2	Phase I
JSI-1187*	MAP2K1,MAP2K2	Phase I
KA2237*	PIK3CB,PIK3CD	Phase I
KA2507*	HDAC6	Phase I&II
Kanitinib*	MET,KDR	Phase I
KB-0742*	CDK9	Phase I
KD 033*	PDCD1	Phase I
KHK 2823*	IL3RA	Phase I
KIN-2787*	BRAF	Phase I
KITE-222*	CLEC12A	Phase I&II
KITE-585*	TNFRSF17	Phase I&II

Drug	Gene Targets	Clinical Phases
KN046*	CD274,CTLA4	Phase I-III
KO-539*	KMT2A	Phase I&II
KPT-9274*	NAMPT,PAK4	Phase I
larotinib*	EGFR,ERBB2,ERBB3,ERBB4	Phase I-III
Lazertinib*	EGFR	Phase I-III
L-DOS 47*	CEACAM6	Phase I&II
Lenzilumab*	CSF2	Phase I-III
Lerociclib*	CDK4,CDK6	Phase I&II
letetresgene	CTAG1B	Phase I&II
Lifirafenib*	EGFR,BRAF	Phase I&II
Linperlisib*	PIK3CD	Phase I&II
lintuzumab*	CD33	Phase I-III
LM-061*	MET	Phase I&II
LM-302*	CLDN18	Phase I/II
LMB-100*	MSLN	Phase I&II
Lodapolimab*	PDCD1	Phase I
Loncastuximab	CD19	Phase I-III
Lorvotuzumab	NCAM1	Phase I&II
LOXO-305*	BTK	Phase I-III
LP002*	CD274	Phase I&II
LTT462*	MAPK1	Phase I&II
Lucitanib*	FGFR1,FGFR2,FGFR3,FGFR4,PD	Phase I-III
Lumretuzumab*	ERBB3	Phase I&II
Lutetium-177	FOLH1	Phase I-III
LVGN7409*	CD40	Phase I
LXI-15029*	MTOR	Phase I
LY011*	CLDN18	Phase I
LY2874455*	FGFR1,FGFR2,FGFR3,FGFR4	Phase I
LY3022855*	CSF1R	Phase I&II
LY3076226*	FGFR3	Phase I
LY3200882*	TGFBR1	Phase I&II
LY3214996*	MAP3K1,MAPK1	Phase I&II
LY3295668*	AURKA	Phase I&II
LY3300054*	CD274	Phase I
LY3321367*	HAVCR2	Phase I
LY3410738*	IDH1	Phase I
LY3434172*	CD274	Phase I
LY3475070*	NT5E	Phase I
LY3484356*	ESR1	Phase I-III
LY3499446*	KRAS	Phase I/II
LY3537982*	KRAS G12C	Phase I
LYT-200*	LGALS9	Phase I/II
M1774*	ATR	Phase I
M4344*	ATR	Phase I&II
M802*	ERBB2	Phase I
Magrolimab*	CD47	Phase I-III
Masitinib*	KIT,PDGFR,FGFR3,FYN,CSF1R,L	Phase II&III
Mavelertinib*	EGFR	Phase I/II
MAX-40279*	FGFR1,FGFR2,FGFR3,FLT3	Phase I&II
MB 101*	CD19	Phase I-III
MB 102*	IL3RA	Phase I-III
MB 103*	ERBB2	Phase I-III
MB 104*	SLAMF7	Phase I-IV
MCLA 145*	PDCD1	Phase I
MCLA-129*	EGFR,MET	Phase I&II
MCLA-145*	CD274	Phase I
MCS110*	CSF1R	Phase I&II
MCY M11*	MSLN	Phase I
MDG1011*	PRAME	Phase I/II

Drug	Gene Targets	Clinical Phases
MEDI4276*	ERBB2	Phase I
MEN 1112*	BST1	Phase I
MEN1611*	PIK3CA	Phase I&II
Merestinib*	MST1R,MET,FLT3,AXL,MERTK,T	Phase I&II
Metatinib *	BCR,ABL1	Phase I
Mezagitamab*	CD38	Phase I&II
MGCD265*	TEK,MET,MST1R,KDR,CSF1R,AX	Phase I&II
MGD 007*	GPA33	Phase I&II
Mipetresgene	CTAG1B	Phase I
Miransertib*	AKT1,AKT2,AKT3	Phase I&II
mirdametinib*	MAPK1	Phase I&II
mirvetuximab*	FOLR1	Phase I-III
mitazalimab*	CD40	Phase I&II
Mivavotinib*	FLT3,SYK	Phase I&II
MK 2206*	AKT1,AKT2,AKT3	Phase I&II
MK2206*	AKT1,AKT2,AKT3	Phase I-III
MK-4830*	LILRB2	Phase I&II
MK-7684A*	PDCD1	Phase I-III
MM-302*	ERBB2	Phase I
Mobocertinib*	EGFR,ERBB2	Phase I&II
molibresib	BRD2,BRD3,BRD4,BRDT	Phase I&II
Momelotinib*	JAK1,JAK2	Phase I-III
Monalizumab*	KLRC1	Phase I-III
MOR202*	CD38	Phase I&II
mosunetuzumab*	MS4A1	Phase I-III
MP 0250*	KDR,HGF,FLT1,FLT4	Phase I/II
MP 0310*	FAP	Phase I
MP0274*	ERBB2	Phase I
MRG002*	ERBB2	Phase I&II
MRG003*	EGFR	Phase I&II
MRX-2843*	FLT3,MERTK	Phase I&II
MSB2311 *	CD274	Phase I
MT 5111*	ERBB2	Phase I&II
MT-3724*	MS4A1	Phase I&II
MTL-CEBPA*	CEBPA	Phase I&II
Naporafenib*	BRAF,RAF1	Phase I&II
Naptumomab	TPBG	Phase I-III
Naquotinib*	EGFR	Phase I-III
Naratuximab	CD37	Phase I&II
Navicixizumab*	DLL4,KDR,FLT1,FLT4	Phase I
Nazartinib*	EGFR	Phase I-III
Nemiralisib*	PIK3CD	Phase I-III
NG-641 *	FAP	Phase I
NGM707*	LILRB1, LILRB2	Phase I/II
Nimotuzumab*	EGFR	Phase I-IV
ningetinib	MET,KDR,AXL,MERTK,FLT3	Phase I/II
NIS793*	TGFB1	Phase I-III
NJH395*	ERBB2	Phase I
NKX-101 *	KLRK1	Phase I
NMS-03305293*	PARP1	Phase I&II
NMS-03592088*	CSF1R,KIT,FLT3	Phase I/II
NP-137 *	NTN1	Phase I&II
NT 219*	STAT3	Phase I/II
NTX-301*	DNMT1	Phase I&II
NX-2127*	BTK	Phase I
NZV930*	NT5E	Phase I
Obrindatamab*	CD276	Phase II
OBT076*	LY75	Phase I
Odronextamab*	MS4A1	Phase I&II

Drug	Gene Targets	Clinical Phases
OKT10-B10*	CD38	Phase I
Olafertinib*	EGFR	Phase I/II
oleclumab*	NT5E	Phase I&II
olinvacimab*	KDR	Phase I&II
olmutinib*	EGFR	Phase I&II
olutasidenib*	IDH1	Phase I&II
Olverembatinib*	FLT3,KIT	Phase I&II
OMO 1*	MET	Phase I/II
OMP-305B83*	DLL4,KDR,FLT1,FLT4	Phase I
Onalespib*	HSP90AA1,HSP90AB1	Phase I&II
Onapristone*	ESR1	Phase I&II
onatasertib*	MTOR	Phase I&II
ONC 201*	AKT1,AKT2,AKT3,MAPK1	Phase I&II
ONC 206*	DRD2	Phase I
ONO-7579*	NTRK1,NTRK2,NTRK3	Phase I
ONO-7701*	IDO1	Phase I&II
Ontorpacept*	CD47	Phase I&II
Onvansertib*	PLK1	Phase I-III
opaganib*	SPHK2	Phase I-III
Oportuzumab*	EPCAM	Phase I-III
orelabrutinib*	BTK	Phase I-IV
Orvacabtagene	TNFRSF17	Phase II
OS 2966*	ITGB1	Phase I
OTS 167*	MELK	Phase I&II
Paclitaxel	LRP1	Phase I-III
Pacmilimab*	PDCD1	Phase I&II
Pacritinib*	FLT3,JAK2	Phase I-III
Pamiparib*	PARP1,PARP2	Phase I-III
Pamufetinib*	MET,KDR,FLT1,FLT4	Phase I&II
Parsaclisib*	PIK3CD	Phase I-III
Patidegib*	SMO	Phase I-III
patritumab*	ERBB3	Phase I-III
Paxalisib*	PIK3CA,PIK3CB,PIK3CD,PIK3CG	Phase I-III
PBI-200*	NTRK1,NTRK2,NTRK3	Phase I/II
PC14586*	p53	Phase I/II
pelabresib*	BRD2,BRD3,BRD4,BRDT	Phase I-III
pelcitoclax*	BCL2L1,BCL2	Phase I&II
Pemrametostat*	PRMT5	Phase I&II
PEN 221*	SSTR2	Phase I/II
PEN 866*	HSP90AA1,HSP90AB1	Phase I&II
Penpulimab*	PDCD1	Phase II/III
Petosemtamab*	EGFR,LGR5	Phase I
pexmetinib*	MAPK11,MAPK12,MAPK13,MA	Phase I&II
PF-03084014*	NOTCH1,NOTCH2,NOTCH3,NO	Phase I-III
PF-06459988*	EGFR	Phase II
PF-06671008*	CDH3	Phase I
PF-06688992*	ST8SIA1	Phase I
PF-06804103*	ERBB2	Phase I
PF-06873600*	CDK2,CDK4,CDK6	Phase I&II
PF-07104091*	CDK2	Phase II
PF-07209960*	PDCD1	Phase I
PF-07248144*	KAT6A,KAT6B	Phase I
PF-07257876*	CD47	Phase I
PF-07284892*	PTPN11	Phase I
PF-114*	BCR,ABL1	Phase I/II
PHI-101*	CHEK2	Phase I
Pictilisib*	PIK3CA,PIK3CD	Phase I&II
Pidilizumab*	PDCD1	Phase I-IV
Pimasertib*	MAP2K1, MAP2K2	Phase I&II

Drug	Gene Targets	Clinical Phases
Pimitespib*	HSP90AA1,HSP90AB1	Phase I
pimivalimab*	CD274	Phase I
pirotinib*	ERBB2,EGFR,EPHB4	Phase I&II
Plamotamab*	MS4A1	Phase I
PLX2853*	BRD4	Phase I
PLX51107*	BRD1,BRD2,BRD3,BRD4	Phase I&II
PLX8394*	BRAF,RAF1	Phase I&II
PLX9486*	KIT	Phase I&II
PMD-026*	RPS6KA2,RPS6KA1,RPS6KA3,RP	Phase I
Poziotinib*	EGFR,ERBB2	Phase I&II
Praluzatamab	ALCAM	Phase I&II
Prexasertib*	CHEK1	Phase I&II
PRGN-3005 *	MUC16	Phase I
PRI-724*	CTNNB1,CREB1,WNT1	Phase I&II
PRL3-ZUMAB*	PTP4A3	Phase I&II
PRN1371*	FGFR1,FGFR2,FGFR3,FGFR4,CS	Phase I
PRT 543*	PRMT5	Phase I
PRT1419*	MCL1	Phase I
PSB202*	MS4A1	Phase I
PT2385*	EPAS1	Phase I&II
PTC596*	BMI1	Phase I
Pyrotinib*	EGFR,ERBB2	Phase I-III
Q 702*	AXL,MERTK,TNFRSF17	Phase I-III
Q-1802*	CD274,CLDN18	Phase I
QBS10072S*	SLC7A4	Phase I
QL-1209*	ERBB2	Phase I
QLS31901*	CD274	Phase I
Quizartinib*	FLT3	Phase I-III
Radotinib *	PDGFR,SNCAIP	Phase I-III
Ralimetinib*	MAPK1	Phase I&II
RC108*	MET	Phase I&II
RC48-ADC*	ERBB2	Phase I-III
refametinib*	MAP2K1	Phase I&II
REGN 4018*	MUC16	Phase I/II
REGN 5458*	TNFRSF17	Phase I/II
REGN 5668*	MUC16	Phase I/II
REGN5093*	MET	Phase I/II
REGN7075*	EGFR	Phase I&II
Relatlimab*	LAG3	Phase I-III
Repotrectinib *	NTRK1,NTRK2,NTRK3,ALK,SRC,	Phase I&II
retifanlimab*	PDCD1	Phase I-III
Rezivertinib*	EGFR	Phase I-III
RGX-202-01 *	SLC6A8	Phase I
ricolinostat*	HDAC6	Phase I&II
Rigosertib*	BCR,ABL1,PLK1,PLK2,PDGFR,SR	Phase I-III
RLY-1971*	PTPN11	Phase I
RLY-4008*	FGFR2	Phase I
RMC4630*	PTPN11	Phase I&II
RMC-4630*	PTPN11	Phase I&II
RMC-5552*	MTOR	Phase I
RO 7122290*	FAP	Phase I/II
RO 7172508*	CECAM5	Phase I
RO 7227166*	CD19	Phase I
RO5126766*	MAP2K1	Phase I&II
RO6870810*	BRD2,BRD3,BRD4,BRDT	Phase I
RO6958688*	CECAM5	Phase I&II
RO7051790*	KDM1A	Phase I
RO7122290*	FAP	Phase I/II
RO7227166*	CD19	Phase I

Drug	Gene Targets	Clinical Phases
RO7247669*	PDCD1	Phase I&II
RO7284755*	PDCD1	Phase I
RO7293583*	TYRP1	Phase I
Rociletinib*	EGFR	Phase I-III
Rogaratinib*	FGFR1,FGFR2,FGFR3,FGFR4	Phase I-III
roniciclib*	CDK1,CDK2,CDK4,CDK9	Phase I&II
RP12146*	PARP1,PARP2	Phase I
RP-3500*	ATR	Phase I/II
runimotamab*	ERBB2	Phase I
RVU120*	CDK8,CDK19	Phase I&II
RX 5902*	BCL2,CDKN1A	Phase I/II
RXC004*	PORCN	Phase I&II
RXC-004 *	WNT1	Phase I&II
sabatolimab*	HAVCR2	Phase I-III
Samotolisib*	PIK3CA,PIK3CB,PIK3CD,PIK3CG,	Phase I&II
Samuraciclib*	CDK7	Phase I/II
Sapanisertib*	CTRC	Phase I&II
Sapitinib*	EGFR	Phase I&II
SAR 442257*	CD38	Phase I
SAR125844*	MET	Phase I&II
SAR428926*	LAMP1	Phase I
SAR439459*	TGFB1	Phase I&II
SAR443216*	ERBB2	Phase I
Saracatinib*	SRC,ABL1	Phase I-III
Sasanlimab*	PDCD1	Phase I-III
Savolitinib*	MET	Phase I-III
SBT6050*	ERBB2,EGFR	Phase I
SC10914*	PARP1,PARP2	Phase I&II
SCT200*	EGFR	Phase I&II
seclidemstat*	KDM1A	Phase I/II
Selitrectinib*	NTRK1,NTRK2,NTRK3	Phase I&II
Serabelisib*	PIK3CA	Phase I&II
Seribantumab*	ERBB3	Phase I&II
serplulimab*	PDCD1	Phase I-III
Sevacizumab*	KDR,FLT1,FLT4	Phase I
SF1126*	PIK3CA,PIK3CB,PIK3CD,PIK3CG,	Phase I&II
SG301*	CD38	Phase I
SGT-53*	TP53	Phase I&II
SH-1028 *	EGFR	Phase I-III
SH3809*	PTPN11	Phase I
SHR1701*	CD274	Phase I-III
SHR2554*	EZH2	Phase I&II
Shr3680*	AR	Phase I-III
SHR7390*	MAP2K1	Phase I&II
SHR-A1811*	ERBB2	Phase I&II
SI-B001*	EGFR,ERBB3	Phase I-III
Silmitasertib*	CSNK2A1	Phase I&II
SIM1803-1A*	NTRK1,NTRK2,NTRK3,ROS1,AL	Phase I
Simlukafusp alfa*	FAP	Phase I&II
Simurosertib*	CDC7	Phase I&II
Sintilimab*	PDCD1	Phase I-III
Siremadlin*	MDM2	Phase I&II
Sitravatinib*	EPHB1,AXL,MET,MERTK,MST1R	Phase I-III
SKB-264 *	TACSTD2	Phase I/II
SKLB1028*	EGFr,FLT3,ABL1	Phase I-III
SLC-391*	AXL	Phase I
SNDX-5613*	KMT2A	Phase I/II
SNX-5422 *	HSP90AA1,HSP90AB1	Phase I&II
Socazolimab*	PDCD1	Phase I-III

Drug	Gene Targets	Clinical Phases
SOR-C13*	TRPV6	Phase I
Spartalizumab*	CD274	Phase I-III
Spebrutinib*	BTK	Phase I&II
SRA737*	CHEK1	Phase I/II
SRF 617*	ENTPD1	Phase I
SRF617*	ENTPD1	Phase I
Stenoparib*	PARP1,PARP2,TNKS	Phase I&II
STI-1492*	CD38	Phase I
STI-6129*	CD38	Phase I
Surufatinib*	KDR,FGFR1,CSF1R,FLT1,FLT4	Phase I-III
SX682*	CXCR1,CXCR2	Phase I&II
SX-682*	CXCR1,CXCR2	Phase I&II
SXL01*	AR	Phase I
SY-1365*	CDK7	Phase I
SY-5609*	CDK7	Phase I
SYHA1801*	BRD4	Phase I
Sym015*	MET	Phase I/II
SYN004*	EGFR	Phase I&II
SYN125*	PDCD1	Phase I
T-1101*	PCSK2	Phase I
TAC01-CD19*	CD19	Phase I/II
TAK 007*	CD19	Phase II
TAK 169*	CD38	Phase I
TAK 573*	CD38	Phase I&II
TAK-164*	GUCY2C	Phase I
TAK-580*	ARAF,BRAF,RAF1	Phase I&II
Talacotuzumab*	IL3RA	Phase I-III
taletrectinib*	NTRK1,NTRK2,NTRK3,ROS1	Phase II
TAS0612*	AKT1,AKT2,AKT3,RPS6KA1,RPS	Phase I
TAS0728*	ERBB2	Phase I/II
TAS0953/HM06*	RET	Phase I/II
TAS-117*	AKT1,AKT2,AKT3	Phase II
TAS2940*	ERBB2,EGFR	Phase I
taselisib*	PIK3CA	Phase I-III
Tebentafusp*	PMEL	Phase I&II
telisotuzumab	MET	Phase I-III
Telomelysin*	TERT	Phase I&II
tenalisib*	PIK3CD,PIK3CG	Phase I&II
Tepoditamab*	CLEC12A	Phase I
Tesevatinib*	ERBB2,EGFR,EPHB4	Phase I&II
TG-1801*	CD47,CD19	Phase I
Tipifarnib*	CXCL12	Phase I-III
Tirabrutinib*	BTK	Phase I&II
Tislelizumab*	PDCD1	Phase I-III
tivantinib*	MET	Phase I-III
TK 216*	FLI1,ETS1	Phase I&II
TL-895*	BTK	Phase I&II
TNB-383B*	TNFRSF17	Phase I
TNB-486*	CD19	Phase I
TNB-585*	FOLH1	Phase I
TNO155*	PTPN11	Phase I&II
Tolinapant*	XIAP,BIRC2	Phase I&II
tomivosertib*	MKNK1,MKNK2,PDCD1	Phase I&II
Toripalimab*	CD274	Phase I-III
TP 1287*	CDK9	Phase I
TP-0184*	ACRV1	Phase I&II
TPX-0022*	MET,SRC,CSFR1	Phase I
TPX0046*	SRC,RET	Phase I/II
TPX-0046*	RET,SRC	Phase I/II

Drug	Gene Targets	Clinical Phases
TQ-B211*	ERBB2	Phase III
TQB2450*	CD274	Phase II
TQ-B3101*	ALK,ROS1,MET	Phase I&II
TQ-B3139*	ALK,MET	Phase I-III
TQB3303*	CDK4,CDK6	Phase I
TQB3455*	IDH2	Phase I
TQB3525*	PIK3CA,PIK3CD	Phase I/II
TQ-B3525*	PIK3CA,PIK3CD	Phase I&II
TQB3616*	CDK4,CDK6	Phase I&II
TQB3823*	PARP1,PARP2	Phase I
TQB3909*	BCL2	Phase I
TR1801-ADC*	MET	Phase I
Trabedersen*	TGFBR2	Phase I-III
TRC253*	AR	Phase I/II
Tremelimumab*	CTLA4	Phase I-III
Triciribine	AKT1,AKT2,AKT3	Phase I&II
TRPH-222*	CD22	Phase I
TT-00420*	AURKA,AURKB	Phase I&II
TTI-101*	STAT3	Phase I
TTI-621*	CD47	Phase I&II
TTI-622*	CD47	Phase I
TTX 030*	ENTPD1	Phase I
Tucidinostat*	HDAC1,HDAC2,HDAC3,HDAC10	Phase I-IV
TVB-2640*	FASN	Phase I&II
TY-9591*	EGFR	Phase I
Ublituximab*	MS4A1	Phase I-III
Uliledlimab*	NT5E	Phase I&II
Ulixertinib*	MAPK3,MAPK1	Phase I&II
Ulocuplumab*	CXCR4	Phase I&II
Unesbulin*	BMI1	Phase I
Vactosertib*	TGFBR1	Phase I&II
Varlilumab*	CD27	Phase I&II
Varlitinib*	EGFR,ERBB2	Phase I-III
VC004*	NTRK1,NTRK2,NTRK3	Phase I/II
Veliparib*	PARP1,PARP2	Phase I-IV
VG161*	PDCD1	Phase I
Vibecotamab*	IL3RA	Phase I
vimseltinib*	CSF1R	Phase I-III
VIP152*	CDK9	Phase I
vistusertib*	MTOR	Phase I&II
VLS-101*	ROR1	Phase I&II
VLX1570*	UCHL5,USP14	Phase I
VMD-928*	NTRK1	Phase I
Vofatamab*	FGFR3	Phase I-IV
vorasidenib*	IDH1,IDH2	Phase I&III
Vorolanib*	PDGFRA,PDGFRB,KDR,FLT1,FLT	Phase I-III
VS 6766*	MAP2K1,RAF1	Phase I&II
VT30*	PIK3CA	Phase I/II
VT3989*	TEAD1,TEAD2,TEAD3,TEAD4	Phase I
vudalimab*	PDCD1	Phase I&II
Vulinacimab*	KDR	Phase I
W0101*	IGF1R	Phase I
WP1066*	JAK2	Phase I
WSD0922-FU*	EGFR,EGFR	Phase I
Xevinapant*	BIRC2,BIRC3,XIAP	Phase I-III
XL 092*	MET,KDR,FLT1,FLT4	Phase I
XL888*	HSP90AA1,HSP90AB1	Phase I
XmAb18087*	SSTR2	Phase I&II
XMT-1522*	ERBB2	Phase I

Drug	Gene Targets	Clinical Phases
XY0206*	FLT3	Phase I
XZP-3287*	CDK4,CDK6	Phase I-III
XZP-5809-TT1*	EGFR	Phase I
XZP-5955*	ROS1,NTRK1,NTRK2,NTRK3	Phase I/II
YS 110*	DPP4	Phase I/II
YYB101*	MET	Phase I&II
Zanidatamab*	ERBB2,SEM1	Phase I&II
ZB716*	ESR1	Phase I/II
ZEN003694*	BRD2,BRD3,BRD4,BRDT	Phase I&II
Zenocutuzumab*	ERBB2,ERBB3	Phase I&II
Zimberelimab*	PDCD1	Phase I-III
ZN-A-1041*	ERBB2	Phase I
ZN-c3*	WEE1	Phase I&II
ZN-e4*	EGFR	Phase I/II
Zolbetuximab*	CLDN18	Phase I-III
Zorifertinib*	EGFR	Phase I-III
Zotatifin*	EIF4A1	Phase I&II
Zotiraciclib*	CDK1,CDK2,CDK7,CDK9,JAK2,FL	Phase I&II
ZW 49*	ERBB2	Phase I
ZX-101A*	PIK3CD,PIK3CG	Phase I/II
ZZ06*	EGFR	Phase I

4.2 Cancer entities and their targeted pathways

After identifying major pathway alterations in oncogenic signaling the next step is to recognize that there are differences concerning pathway and gene alterations in distinct cancer types. A study of Sanchez-Vega et al.(Sanchez-Vega et al., 2018) profiled various individual cancer types and their typical pathway alterations with data available from The Cancer Genome Atlas (TCGA). 98% of the cancer entities displayed one or more mutations or modification in a driver gene, with 57% of all tumors presenting presently targetable alterations. For this study the following ten pathways were investigated: cell cycle, Notch, PI3K/Akt, RTK-RAS, TGFb signaling, p53, beta-catenin/Wnt, Mc and Nrf2 pathways. According to the pathways identified in 2.2.3 and based on cancer types as specified by the datasets of TCGA, Table 7 present an overview over different cancer entities and the number of target genes used in targeted therapies for each pathway. Since target genes are involved in various pathways the sum of target genes doesn't match the total per cancer entity, but a total is also given for each type. The Table 7 identifies each target gene separately for all cancer types.

Table 7 showing cancer entities and the number of target genes for each pathway in cancer according to KEGG database.

	Cancer entities	pathways																											
		cancer	Adherens junctions	Apoptosis	Calcium	cAMP	Cell cycle	cytokine-cytokine	ECM-receptor	Estrogen	focal adhesion	hedgehog	HIF-1	Jak-STAT	MAPK	mTOR	NOTCH	p53	PI3K-Akt	PPARP	TGF-b	VEGF	Wnt#	base excision repair	Erbb	Ras	Other	sum	
CNS	Glioma	14	5	5	5	5	6	7	4	5	8	1	9	10	12	9	4	7	15	1	4	10	7	1	11	11	26	54	CNS
	Medulloblastom	1	0	0	0	0	0	0	0	0	0	0	1	1	2	1	0	1	2	0	0	1	1	0	1	1	3	8	
	Brain Cancer	12	4	5	3	3	5	10	3	4	10	0	8	8	9	8	6	7	11	1	6	8	7	2	8	8	21	47	
	Glioblastoma	19	5	6	4	4	7	11	4	5	13	1	10	11	16	10	5	9	22	1	5	11	8	1	13	14	43	75	
	Astrocytoma	9	1	1	1	1	1	5	1	1	5	1	4	4	6	4	1	3	7	1	1	4	3	1	5	5	10	19	
	Oligodendroglioma	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	0	0	1	1	0	1	1	1	2	
	Meningioma	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	0	1	1	0	0	1	1	0	1	1	2	4	
	total	24	6	7	5	5	8	13	4	6	15	1	14	15	20	14	7	11	28	1	7	15	10	2	17	18	53	100	
Eye	Olucar Melanoma	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	Eye
	Retinoblastoma	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
	Eye	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0	1	1	
	total	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0	1	1	
Head and Neck	Head and Neck Squamous Cell Ca	4	1	1	0	0	1	1	0	1	3	0	2	2	2	2	1	2	4	1	1	2	2	1	2	2	8	26	Head and Neck
	Nasopharyngeal Carcinoma	5	3	3	3	3	3	3	3	3	4	0	6	6	6	6	4	6	9	1	4	6	6	1	6	6	12	23	
	Salivary Carcinoma	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	5	
	Head and Neck	19	7	8	5	5	10	10	5	6	12	1	6	7	9	6	4	6	14	1	4	7	6	1	8	9	30	74	
	total	19	7	8	5	5	10	10	5	6	12	1	6	7	9	6	4	6	15	1	4	7	6	1	8	9	33	78	
Endocrine	Adrenal Gland	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	0	1	4	0	0	1	1	0	1	1	4	11	Endocrine
	Thyroid	7	3	3	3	3	3	4	3	3	5	0	6	6	8	6	4	6	11	1	4	6	6	1	6	7	14	33	
	Endocrine	7	4	4	3	3	4	4	3	4	4	0	5	5	8	5	3	5	10	0	3	6	5	0	6	7	16	29	
	total	9	4	4	3	3	4	5	3	4	6	0	6	6	9	6	4	6	13	1	4	7	6	1	7	8	19	40	
Thymus	Thymoma	3	1	1	1	1	1	1	1	1	2	1	1	1	2	1	0	1	3	0	0	1	1	0	1	2	6	12	Thymus
	Thymic	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	5	
	total	3	1	1	1	1	1	1	1	1	2	1	1	1	2	1	0	1	3	0	0	1	1	0	1	2	6	13	
Thoracic	Lung	43	10	15	7	7	17	23	6	9	27	1	15	16	24	13	8	11	35	1	8	16	10	3	18	21	76	155	Thoracic
	Non-Small Cell Lung Cancer	39	10	13	7	7	15	20	6	9	24	1	13	14	21	13	8	11	32	1	8	14	10	3	16	18	67	141	
	Lung Adenocarcinoma	1	0	0	0	0	0	0	0	0	0	0	2	2	2	2	1	2	4	1	1	2	2	1	2	2	5	5	
	Small Cell Lung Cancer	22	5	9	3	3	9	13	3	4	14	0	9	9	11	8	4	6	14	1	4	9	5	1	9	10	26	49	
	Pleura	7	3	4	1	1	4	4	0	2	6	0	1	1	2	1	0	1	3	0	0	1	1	0	1	2	11	35	
	total	43	10	15	7	7	17	23	6	9	27	1	15	16	24	13	8	11	35	1	8	16	10	3	18	21	76	160	
	Breast	33	9	12	7	7	12	16	6	8	18	2	14	14	17	12	7	10	26	1	7	14	9	2	15	16	66	136	
Core GI	Esophagus	20	6	7	5	5	7	7	4	6	8	1	9	10	12	9	5	8	14	1	5	10	7	2	11	12	32	73	Core GI
	Gastric	19	5	7	4	4	7	8	4	5	9	1	11	12	16	11	6	9	20	1	6	13	8	2	14	15	41	86	
	Colon	4	3	3	3	3	3	3	3	3	4	0	5	5	5	5	4	5	7	1	4	5	5	1	5	5	15	22	
	Colorectal	20	4	5	4	4	7	8	4	4	11	0	9	10	14	8	4	7	19	1	4	11	6	1	12	14	49	103	
	total	35	7	9	6	6	11	13	5	7	17	1	13	14	20	12	7	10	27	1	7	15	9	3	17	19	66	145	
Develop. GI	Biliary tract	13	5	6	3	3	6	7	3	4	8	0	8	8	9	7	5	6	11	1	5	8	6	1	8	9	23	43	Develop. GI
	Liver	12	4	6	4	4	6	6	3	4	10	0	7	8	8	6	4	6	12	1	4	8	6	1	8	8	23	47	
	Pancreas	24	5	6	4	4	6	10	3	5	14	0	11	12	19	11	6	9	23	1	6	13	8	2	15	17	51	107	
	total	31	7	9	5	5	9	14	3	6	19	0	14	15	22	13	7	10	28	1	7	16	9	2	18	20	59	125	
Genitourinary	Bladder Urethlial	10	4	5	3	3	5	5	3	3	7	0	4	4	7	4	4	4	8	0	4	4	4	1	5	6	17	40	Genitourinary
	Renal Cell Carcinoma	13	3	4	3	3	4	4	3	3	7	0	8	9	11	8	5	8	14	0	5	9	7	1	10	11	36	69	
	Rhabdoid	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	0	1	1	0	0	1	1	0	1	1	2	6	
	Wilm's Tumor	1	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	
	Testis	5	3	3	3	3	3	3	3	3	3	0	4	4	5	4	3	4	6	0	3	4	4	0	4	5	9	16	
	total	16	4	5	3	3	5	5	3	3	8	0	10	11	14	10	6	10	18	0	6	11	9	2	12	13	43	85	
Gynecologic	Cervix	7	4	5	3	3	5	5	3	4	6	0	8	8	9	8	4	7	12	1	4	8	6	1	8	9	21	41	Gynecologic
	Uterus	5	3	3	3	3	3	3	3	3	3	0	3	3	3	3	3	3	3	0	3	3	3	0	3	3	6	13	
	Vulva/Vagina	1	0	0	0	0	0	0	0	0	0	0	2	2	3	2	0	1	3	0	0	2	0	0	2	3	3	4	
	Ovarian	30	7	9	6	6	12	16	5	7	18	1	10	11	14	9	6	8	22	1	6	11	8	2	12	13	52	113	
	Fallopian Tube	14	5	6	4	4	6	6	4	5	7	1	8	9	12	8	4	7	17	0	4	9	6	0	10	11	26	52	
	total	30	7	9	6	6	12	16	5	7	18	1	12	13	16	11	6	9	24	1	6	13	8	2	14	15	55	119	
Skin	Basal Cell Carcinoma	1	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0	3	0	0	0	0	0	0	0	3	8	Skin
	Cutaneous Squamous Cell Carcinoma	6	3	3	3	3	3	3	3	3	6	0	5	5	5	5	5	5	5	0	5	5	5	1	5	5	10	21	
	Melanoma	22	6	7	6	6	7	9	4	6	12	1	13	14	19	13	8	11	23	1	8	15	10	3	16	17	47	107	
	total	24	6	7	6	6	7	9	4	6	14	1	13	14	19	13	8	11	24	1	8	15	10	3	16	17	48	114	
Soft Tissue	Angiosarcoma	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	3	Soft Tissue
	Rhabdomyosarcoma	1	0	0	0	0	0	0	0	0	1	0	3	3	3	3	0	2	4	0	0	3	1	0	3	3	6	11	
	Soft Tissue	7	0	1	0	0	1	1	0	0	2	0	3	3	6	2	1	2	10	0	1	3	2	1	3	4	19	33	
	Paraganglioma	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	0	1	3	0	0	1	1	0	1	1	3	10	
	total	7	0	1	0	0	1	1	0	0	2	0	5	5	8	4	1	3	12	0	1	5	2	1	5	6	22	41	
Bone	Ewing Sarcoma	2	0	1	0	0	1	1	0	0	2	0	4	4	4	4	1	3	7	0	1	4	2	0	4	4	9	22	Bone
	total	2	0	1	0	0	1	1	0	0	2	0	4	4	4	4	1	3	7	0	1	4	2	0	4	4		22	
Heme	Myeloid neoplasms	32	5	10	4	4	11	18	4	4	19	1	10	10	17	9	5	6	21	1	5	10	6	1	14	16	51	107	Heme
	myeloproliferative neoplasm	4	0	0	0	0	0	4	0	0	4	0	4	4	6	4	0	1	6	0	0	4	1	0	4	4	8	11	
	acute myeloid Leukemia	31	5	9	4	4	10	17	4	4	18	1	10	10	16	9	5	6	19	1	5	10	6	1	14	15	49	104	
	Myelodysplastic syndromes	22	5	7	4	4	7	12	4	5	13	1	7	7	12	7	3	4	18	0	3	7	4	0	11	11	39	71	
	Lymphoid neoplasms	6	3	3	3	3	3	3	3	3	5	0	6	6	6	6	4	5	7	0	4	6	4	0	6	6	11	21	
	Non Hodgkin Lmyphoma	25	6	8	5	5	8	13	4	6	18	1	10	10	14	9	6	8	18	1	6	10	8	2	12	12	40	80	
	Hodgkin	5	0	0	0	0	0	0	0	0	3	0	0	0	3	0	0	0	3	0	0	0	0	0	2	2	6	11	
	B-Cell Lymphoma	11	4	4	4	4	4	6	4	4	8	1	9	9	9	9	6	8	10	0	6	9	8	1	9	9	22	35	
	T-Cell Lymphoma	5	3	3	3	3	3	3	3	3	4	0	5	5	6	5	5	5	7	0	5	5	5	1	5	5	10	15	
	Myeloma	21	3	5	3	3	5	8	3	3	9	0	10	10	12	10	7	9	15	0	7	11	9	1	12	12	34	75	
	total	49	8	14	6	6	15	22	5	7	27	2	17	17	26	16	9	12	35	1	9	18	11	2	22	24	84	176	

Pathways in cancer
Adherens junctions
Apoptosis
Calcium signaling pathway
cAMP signaling pathway
Cell cycle
cytokine-cytokine signaling pathway
ECM-receptor
Estrogen signaling pathway
focal adhesion
hedgehog signaling pathway
HIF-1 signaling pathway
Jak-STAT signaling pathway
MAPK signaling pathwa
mTOR signaling pathway
NOTCH signaling pathway
p53 signaling pathway
PI3K-Akt signaling pathway
PPAR signaling pathway
TGF-b signaling pathway
VEGF signaling pathway
Wnt signaling pathway
base excision repair
Erbb pathway
Ras signaling pathway
Other
SUM of target genes

Pathways

4.3 Target therapies in gastric cancer

Following the investigation of all cancer types and their targeted pathways/target genes, targeted therapies in clinical trials for gastric cancer are demonstrated in detail subdivided by the definitions of 0 in alphabetical order.

4.3.1 Apoptosis inducer

Apoptosis is defined as programmed cell-death, which is thoroughly regulated through different processes and a method for a multi cell organism to maintain homeostasis. Cells move into apoptosis infidelities or a failure of quality of proliferation are detected in a cell's life cycle. Apoptosis is among others regulated by serine proteases known as caspases and the p53 dependent apoptotic pathway which reacts to stimulants like DNA damage, lack of oxygen or the manifestation of oncoproteins like Ras or Myc. Since cancer cells often induce processes to avoid apoptosis and activate unregulated proliferation, these targets are investigated extensively in cancer research. Three targeted therapies with three different target genes were recognized in trials open for patients with gastric cancer targeting apoptosis(X. Xu et al., 2019).

Table 8 Apoptosis inhibitors in clinical trials for gastric cancers.

Apoptosis inducer			
1	APG 115	MDM2	Apoptosis inducers
2	Eprenetapopt	p53	Apoptosis inducers
3	IGM-8444	TNFRSF10B	Apoptosis inducers

APG-115 is a small molecule inhibitor of *MDM2* (murine double minute 2)(Fang et al., 2021). *MDM2* is the main suppressing regulator of p53 and a target for p53 restoration to increase radiosensitivity or to increase effects of immune modulation in combination with PD-1 blockade. There was one clinical trial completed in 2019 (NCT02935907) but unfortunately no results were published. Currently there are six recruiting trials investigating APG-115 in combination with PD-1 inhibitors and/or chemotherapy mostly in lymphomas and other hematologic cancers in phases I and/or II (NCT04496349, NCT04785196, NCT04358393, NCT03611868, NCT03781986, NCT04275518).

Eprenetapopt (APR-246) is a pro drug that after conversion binds to Cys residues in mutant p53 and reinstates protein function. In a phase II clinical trial eprenetapopt combined with azacitidine for patients with myelodysplastic syndromes and acute myeloid leukemia (AML) with mutant forms of *TP53* showed non-significant higher ORR and OS than in the group treated with azacitidine alone(Cluzeau et al., 2021). A phase Ib/II clinical study including patients with esophageal cancer exposed that the expression of solute carrier family 7 member 11 (SLC7A11is a supreme determinant of the sensitivity to APR-246 compared to the mutational status of *TP53(Fujihara et al., 2021)*. Unfortunately, the funding for this trial (NCT02999893) concerning esophageal cancer was terminated due to ceased funding.

Currently there is only one active trial, a phase III clinical trial (NCT03745716) investigating APR-246 combined with azacitidine for the treatment of *TP53* mutant myelodysplastic syndromes (MSD). APR-246 also showed encouraging results for in vitro diffuse-type gastric cancer. It can inhibit an increased amount of glutathione by upregulated SLC7A11. SLC7A11 can be elevated by a chromatin remolding complex, ARID1A. If ARID1A is defective in diffuse-type gastric cancer APR-246 leads to reduced glutathione levels and to an exorbitant production of reactive oxygen species(Sasaki et al., 2020). Further investigations are still needed.

IGM-8444 is an immunoglobulin M (IgM) antibody targeting the death receptor 5 (DR5) that can instigate apoptosis in cancer cells. DR5 is a receptor that is widely upregulated and expressed in cancer cells and thereby depicts an appealing target for targeted therapies. In hematologic cancer cell lines IGM-8444 displayed cytotoxicity and lead to the phase I clinical trial (NCT04553692) investigating relapsed and/or refractory solid cancers, including gastric cancer, either as a monotherapy or in combination with chemotherapy or other drugs like bevacizumab. The study is expected to be completed in October 2023.

4.3.2 DNA damage

DNA repair and DNA-damage response is a significant element of a cells natural defence to ensure a proper functional stability and avoid gathering of oncogenic mutations. Certain germline mutation like BRCA1 and 2, TP53, RAD51C, and MSH2 cause in increased vulnerability to the development of cancer. Cancer cells frequently maintain a decreased range of DNA repair mechanisms compared to ordinary cells and occasionally even mutated repair pathways driving oncogenesis(Brown, O'Carrigan, Jackson, & Yap, 2017).

Table 9 DNA damage response and repair targeting drugs in clinical trials for gastric cancer.

DNA damage			
4	PEN 866	HSP90AA1,HSP90AB1	DNA Damage
5	Camidanlumab tesirine	IL2RA	DNA Damage
6	Fluzoparib	PARP1,PARP2	DNA Damage
7	Vendaparib	PARP1,PARP2	DNA Damage
8	Veliparib	PARP1,PARP2	DNA Damage
9	RGX-202-01	SLC6A8	DNA Damage
10	QBS10072S	SLC7A5	DNA Damage
11	Telomelysin	TERT	DNA Damage

PEN-866 is a drug conjugate connecting HSP90, which is often overexpressed in various cancer entities, to a SN-83 cytotoxic payload. In preclinical models it showed full cancer regression and is being currently tested in two phase I/II clinical trials (NCT03221400,

NCT04890093). First results of the phase I trial, including gastric cancer, were published in 2020 showing antitumor activity and a high tolerance to the treatment(Falchook et al., 2020). Next results are expected in June 2023.

Camidanlumab tesirine (ADCT-301) is an antibody drug conjugate that consist of an antibody against CD25 and pyrrolobenzodiazepine dimer toxin that is released into the cell after binding to CD25. CD25, which is the alpha chain of the interleukin 2 receptor (IL2RA), is widely expressed in hematologic cells of hematological malignancies and other cancer entities. A phase I clinical trial including relapsed and refractory lymphoma presented reasonable side effect profiles with antitumoral activity especially in classical Hodgkin lymphoma with an overall response rate of 71% (95% CI 60-81)(Hamadani et al., 2021). Momentarily there is a phase I clinical trials recruiting for patients with advanced solid tumours with literature evidence of CD25 positive content including gastric cancer (NCT03621982). This study combines ADCT-301 with Pembroliuzmab with first results expected in November 2023.

Fluzoparib (SHR-3162), **Vendaparib** (IDX-1197), and **Veliparib** (ABT-888) are novel PARP1/PARP2 inhibitors currently in clinical trials. The first-generation PARP inhibitor Olaparib displayed a hematological toxicity that novel PARP inhibitors are trying to eradicate and additionally provide a simpler application. **Fluzoparib** mainly inhibits the PARP1 enzyme while causing DNA double-strand breaks as well as cell cycle arrest and apoptosis in cell that showed a deficiency in homologous recombination repair(L. Wang et al., 2019). There were first promising results, especially in breast and ovarian cancer with germline mutation in *BRCA1/2*(Han et al., 2019; N. Li et al., 2021), but it also enhances radiation sensitivity in non-small lung cancer without BRCA1/2 mutation(Luo et al., 2020) or in biliary tract cancer cells(Zhu et al., 2020). In a phase I clinical trial (NCT03026881) patients with gastric cancer received fluzoparib combined with apatinib and/or paclitaxel. Unfortunately, it hasn't published any results yet, although it was started in 2017 and is marked with a status as 'unknown'. **Vendaparib** on the other hand hasn't presented any clinical data yet. There are currently three trials recruiting participants, one of them focusing on patients with advanced gastric cancer treated with Vendaparib either in a combination with XELOX or Irinitecan. First results are expected in December 2023. **Veliparib** is a targeted therapy that was or is currently investigated in over a hundred different clinical trials with the main focus on ovarian cancer awaiting FDA approval for a few years now(Boussios et al., 2020). Patients with gastric cancer were included in three phase I clinical trials evaluating safety and tolerability of Veliparib in patients with solid advanced cancers, but no further trials have been pursued since then.

RGX-202-01 is a solute carrier family 6 member 8 (SLC6A8) transporter inhibitor that regulates creatinine levels and presented antitumor activity in vivo and in vitro of colorectal cancers. SLC6A8 is linked to increased risk for colorectal cancer, and it was reported that SLC6A8 which is a protein for the creatin transporter has a protective effect on cancer cells. An

overexpression of SLC6A8 leads to higher levels of intracellular creatin which is adaption to higher demand of energy(Q. Li et al., 2021). RGX-202-01 is now in a trial as a single agent and/or as a combination with FOLFIRI and/or bevacizumab for gastrointestinal malignancies and results are expected by the end of 2022 (NCT03597581).

QBS10072S is a selective inhibitor for the amino transporter type 1 (also known as LAT1) which is responsible for the transportation of essential amino acids. LAT1/SLC7A5 is very low expressed in normal tissue but highly expressed in cancer tissue for a higher demand for proliferation of cancer tissue. There are currently three clinical trials, one of them, a phase I clinical trial, including gastric cancer and other solid cancer entities (NCT04430842). There is another two phase II clinical trials that focus on glioblastoma (NCT02977780) and brain metastases originated from breast cancer (NCT05305365). Two preclinical studies showed efficacy against those two malignancies, brain metastasis(J. Deng et al., 2021) and glioblastoma(Ozawa et al., 2021).

Telomelysin (OPB-301) consists of an adapted type-5 adenovirus including the humane reverse transcriptase promotor to modulate viral replication. After application telomelysin stimulates radiation sensitivity of human cancer cells by interfering with DNA repair. There were two successful phase I trials, one including patients with esophageal cancer(Shirakawa et al., 2021) combined with radiotherapy and one for other various solid tumors(Nemunaitis et al., 2010). In the phase I dose escalation trial telomelysin was injected via an endoscope three times on days 1, 18, and 32 while radiotherapy was applied constantly over 42 days starting on day 4 with a sum of 60 Gy (Gray). The objective response rate (ORR) was 91.7% with 8 patients experiencing a complete response(Shirakawa et al., 2021). There are currently two trials performed recruiting for patients with esophagogastric adenocarcinoma. One of them is a phase I clinical trial ffor patients who are not suitable for surgery and receive telomylesin in addition to chemoradiation NCT04391049). The other is a phase II clinical trial investigating telomylesin in combination with pembrolizumab, an PD-1 inhibitor (NCT03921021). One more clinical phase II trial is momentarily active inquiring telomelysin in combination with pembrolizumab as well, but on squamous cell carcinomas of the head and neck (NCT04685499).

4.3.3 Immunotherapy

Therapies utilizing the patient's own immune systems to attack malignancies are so called immunotherapies. There are already therapies approved by the FDA especially PD-L1 (also known as *CD274*) and PD-1 (*PDCD1*) inhibitors. The following targeted therapies are in clinical trials including patients with gastric cancer of drugs that haven't been approved by the FDA yet for any other cancer entity or gastric cancer.

i. Immune checkpoint inhibitors

Immune checkpoint inhibition decreases the immune system's resistance to tumor cells with a blockade of the PD-L1 and PD-1 interaction. By binding to PD-1 apoptosis in antigen specific T-cells is suppressed and recovers the successful identification and elimination of cancer cells by preventing T-cell inhibition. Due to a other immunosuppressive elements especially in the tumor microenvironment or T-cell exclusion as well as insufficient T-cell trafficking up to 60% of patients show little to no response to a PD-1 inhibition(Song, Chen, Wang, & Zhang, 2018).

Table 10 Immunotherapies in clinical trials containing patients with gastric cancer.

			Immunotherapy
Immune checkpoint inhibitors targeting PD-1/PD-L1			
12	CDX-527	CD274	Immunotherapy
13	IMC001	CD274	Immunotherapy
14	SHR1701	CD274	Immunotherapy
15	Spartalizumab	CD274	Immunotherapy
16	Toripalimab	CD274	Immunotherapy
17	TQB2450	CD274	Immunotherapy
18	KN046	CD274,CTLA4	Immunotherapy
19	Camrelizumab	PDCD1	Immunotherapy
20	Envafolimab	PDCD1	Immunotherapy
21	retifanlimab	PDCD1	Immunotherapy
22	Sasanlimab	PDCD1	Immunotherapy
23	serplulimab	PDCD1	Immunotherapy
24	Sintilimab	PDCD1	Immunotherapy
25	Tislelizumab	PDCD1	Immunotherapy
26	vudalimab	PDCD1,CTLA4	Immunotherapy
27	AK104	PDCD1,CTLA4	Immunotherapy
Other immunotherapies			
28	Sotigalimab	CD40	Immunotherapy
29	CDX-1140	CD40	Immunotherapy
30	LVGN7409	CD40	Immunotherapy
31	Zolbetuximab	CLDN18	Immunotherapy
32	MCS110	CSF1R	Immunotherapy
33	Tremelimumab	CTLA4	Immunotherapy
34	Catumaxomab	EPCAM	Immunotherapy
35	Epacadostat	IDO1	Immunotherapy
36	NGM707	LILRB1, LILRB2	Immunotherapy
37	PRL3-ZUMAB	PTP4A3	Immunotherapy
38	INBRX-105	TNFRSF9,PDCD1	Immunotherapy
39	Ceralasertib	ATR	DNA Damage
40	Elimusertib	ATR	DNA Damage

CDX-527 is a bispecific antibody targeting PD-L1 and CD27, that is intended to inhibit immune checkpoint PD-L1/PD-1 interaction and the same time deliver immune stimulation through CD27 signalling. CD27 improves T cell activation, survival and effector activity. A phase I clinical trial including gastric cancer displayed high tolerance for CDX-527 and only adverse advents like influenza-like illness and arthralgia(Sanborn et al., 2021).

PD-1 one the other hand is the counterpart receptor on cells of the immune system, namely T-cells.

IMC-001 is a human monoclonal antibody that binds to PD-L1. A first phase I study displayed tolerable adverse effects and first effects on the 15 patients enrolled with one partial response and a disease control rate of 33.3%(Keam et al., 2021). Among others there is a phase II clinical trial investigating patients with resectable gastrointestinal cancers including resectable and localized gastric cancer (NCT04196465). Participants receive two cycles of neoadjuvant IMC-001 treatment before tumor resection with a close follow up after. First results are expected for September 2026.

SHR-1701 is a bifunctional fusion protein consisting of a monoclonal antibody against PD-L1 combined with a TGF-β II receptor. A first phase I clinical trial for patients with EGFR positive non-small cell lung cancer (NSCLC). The trial displayed a manageable safety profile for SHR-1701 with first efficacy on NSCLC(M. Shi et al., 2021). Similar results were demonstrated by a phase I clinical trial on patients with recurrent or metastatic cervical cancer. An overall response rate of 15.6% (95%CI, 5.3 – 32.8) and a disease control rate of 50.0% (95% CI, 31.9 - 68.1) was achieved(Feng et al., 2022). By now there are 27 active trials researching SHR-1701 including a randomized, double blind phase III clinical trial for patients with HER2 negative gastric and gastroesophageal cancer. One treatment arm will receive SHR-1701 combined with either the CAPOX regime, consisting of oxaliplatin and capecitabine, or the FOLFOX regime, oxaliplatin, leucovorin and fluorouracil, with the other arm receiving a placebo instead of SHR-1701. Results are expected in June 2025.

Spartalizumab (PDR001) is monoclonal antibody with high affinity to PD-L1 to block the interaction between it and PD-1. Previous studies have shown a tolerable safety profile with adverse effects like fatigue, diarrhea and pruritus(Naing et al., 2020). The GASPAR trial is an open-label multicenter, but not randomized phase II clinical trial investigating safety and efficacy of PDR-001 in a perioperative setting for resectable gastric cancer and adenocarcinoma of the gastro-esophageal junction combined with the FLOT regimen (NCT04736485)(Dos Santos et al., 2022). First results are expected in March 2023 with the end of study in 2027.

TQB2450 is a novel PD-L1 antibody which was investigated for locally advanced or metastatic soft tissue sarcoma in a single arm phase II trial(J. Liu et al., 2022) and in phase Ib clinical trial for pretreated advanced biliary tract cancer both in combination with anlotinib, a VEGFR

inhibitor(Zhou et al., 2022). The studies displayed encouraging efficacies and safety profiles for the considered cancer entities. There is a single arm phase II clinical trial for patients with locally advanced, recurrent or metastatic gastric cancer or adenocarcinoma of the GEJ analysing a treatment with TQB2450, anlotinib with a CapeOx regime (NCT04891900).

KN046 is a bispecific recombinant humanized antibody targeting both PD-L1 and CTLA-4, which is attached to a newly developed delivering system F-ZIF-8 to reduce usual side effects of immune checkpoint inhibitors and allow for a wider use(C. Jiang et al., 2021). There is an open phase I/II clinical trial investigating donafenib in combination with KN046 for advanced gastrointestinal tumors including gastric cancer, esophageal or colorectal cancer with the phase II study focusing on advanced hepatocellular cancer NCT04612712).

Toripalimab (TAB001, JS001) is a humanized antibody targeting PD-1. A first Ib/II clinical trial evaluated the safety and efficacy of Toripalimab in patients with chemotherapy-refractory advanced gastric cancer and analyzed that especially participants with a high mutational burden gained a benefit of the treatment with Toripalimab. In combination with the XELOX regime consisting of oxaliplatin and capecitabine, Toripalimab showed an overall response rate of 66.7% and disease control rate was even 88.9% (F. Wang et al., 2019). There thirteen active clinical trials originating in China right now investigating the toripalimab in patients with gastric cancer, two of them being phase III clinical trials combining toripalimab with a chemotherapy regime. The first one is an international mutlicenter randomized, double blind, phase III clinical trial combining either toripalimab or a placebo with postoperative adjuvant chemotherapy regime of either XELOX or SOX (oxaliplatin and S-1) with the estimated completion date being July 2028 (NCT05180734). The second phase III trial is a multicenter, randomized, controlled study for D2/R0 resected pN3 gastric or GEJ adenocarcinoma testing different the PD-1 inhibitors toripalimab, pembrolizumab, tislelizumab, sintilimab and carrelizumab with a chemotherapy of CapeOx (oxaliplatin and cabecitabine), SOX or FOLFOX. Its end date is expected for October 2021 (NCT04997837). The three PD-1 inhibitors **tislelizumab**, **sintilimab** and **camrelizumab** also being new targeted therapies not yet approved by the FDA. There is one phase I clinical trial examining the safety, tolerability and pharmacokinetics of toripalimab in the U.S. (NCT03474640).

Envafolimab is a novel humanized PD-L1 antibody that has the advantage of a subcutaneous instead of an intravenous injection. It was investigated for defective mismatch repair and microsatellite highly instable solid tumors including gastric cancer in a phase II clinical trial displaying efficacy with an objective response rate of 42.7% (95& CI, 33.0-52.8) and a manageable safety profile(J. Li et al., 2021). Currently there are another two phase II clinical studies, one investigating envafolimab with chemotherapy for metastatic and recurrent gastric adenocarcinoma (NCT05237349) and one for a neoadjuvant treatment for gastric and GEJ adenocarcinoma (NCT05387681).

The monoclonal antibody PD-1 inhibitor **retifanlimab** is part of the phase II/III MAHOGANY trial that assesses margetuximab, a HER2 antibody and tebotelimab, a bispecific antibody binding to PD-1 and LAG-3 (lymphocyte-activation gene) as an alternative standard therapy for unresectable or metastatic gastric or GEJ adenocarcinoma (NCT04082364)(D. V. Catenacci et al., 2021). There is a two arm, randomized, double-blind phase III clinical trial to assess retifanlimab or a placebo in combination with SOX chemotherapy regimen for neoadjuvant and adjuvant treatment of advanced and untreated gastric adenocarcinoma (NCT04139135).

Sasanlimab (PF-06801591) is an PD-1 inhibitor in an early stage of clinical trials with three studies assessing its safety and tolerability for gastric cancer and other solid tumors in the United States (NCT05233436, NCT04254107, NCT04458259) with the focus being on bladder cancer in phase III clinical trial (NCT04165317).

Serplulimab (HLX10) is a fully humanized immunoglobulin G4 antibody increasing T-cell and antitumor activity in in vitro and in vivo models with comparable or better results than to FDA approved pembrolizumab and nivolumab(Issafras et al., 2021).

Tislelizumab a monoclonal antibody against PD-1 was investigated as first line therapy with a CapOx chempotherapy regimen in locally advanced or metastatic esophageal squamous cell carcinoma (ESCC) and gastric or GEJ adenocarcinoma with substantial responses and feasible tolerability(J. Xu et al., 2020). There is a randomized, placebo-controlled, double-blind phase III clinical trial assessing tislelizumab combined with chemotherapy as a first line treatment for locally advanced, unresectable or metastatic gastric or GEJ adenocarcinoma in the U.S. (NCT03777657). The chemotherapy regimen consists of oxaliplatin, capecitabine or cisplatin and 5-fluorouracil.

Sintilimab is another novel highly selective immunoglobulin G4 PD-1 antibody which expressed a high antitumor response in previous trials for locally advanced or metastatic gastric/gastroesophageal junction adenocarcinoma in a phase Ib clinical trial(H. Jiang et al., 2020) and in an early feedback of a phase II for locally advanced resectable GC and GEJ adenocarcinoma with sintilimab in combination with CapOx as neoadjuvant treatment(H. Jiang et al., 2020). There are currently twenty-four studies researching sintilimab. All of them are taking place in China, with three of them being phase III clinical trials. The ORIENT-106 trial analyzes either sintilimab or ramucirumab as a first-line treatment combined with either the XELOX regimen or the FP regimen (Cisplatin and 5-fluorouracil) on patients with HER2 negative and PD-L1 positive unresectable locally advanced or metastatic GC and GEJ adenocarcinoma (NCT04675983). A single arm Phase II/III clinical study investigates sintilimab joined with albumin-paclitaxel/oxaliplatin/capecitabine and radiotherapy accompanied by a D2 resection for advanced GC with retroperitoneal lymph node metastasis

(NCT05002686). The third phase III trial is already mentioned in combination with toripalimab (NCT04997837).

Camrelizumab (SHR-1210) is a selective humanized immunoglobulin G4 monoclonal antibody against PD-1, which has shown promising antitumor activity for recurrent or metastatic gastric and gastro-esophageal adenocarcinoma in a phase I trial(Huang et al., 2019). An open label phase II investigating camrelizumab combined with CapOx with a follow-up of camrelizumab and apatinib as a first-line treatment for advanced and metastatic gastric and gastro-esophageal adenocarcinoma. The ORR for this treatment option was 58.3% (95% CI, 43.2-72.4) with a median duration response of 5.7 months (95% CI, 4.4-8.3)(Peng et al., 2021). There is a double blind, randomized phase III clinical trial of camrelizumab in combination with apatinib in comparison to paclitaxel or irinotecan ongoing researching GC and GEJ adenocarcinoma (NCT04342910).

Vudalimab (XmAb 717) and **AK104** are bispecific antibodies that target PD-1 as well as the CTLA-4. Vudalimab is tested for solid tumors including gastric cancer in a phase I clinical trial to assess its safety and efficacy (NCT03517488). AK104 on the other hand is already investigated as a first line treatment in a double-blind, randomized phase III clinical trial with a XELOX regimen for locally advanced unresectable gastric or GEJ adenocarcinoma (NCT05008783).

ii. Other immunotherapies

Sotigalimab (APX005M), **CDX-1140** and **LVGN7409** are agonistic CD40 antibodies which induce antitumor effects by improving costimulatory molecules and changing the tumor microenvironment as well as activate T-cells. Especially in combination with other treatments like immune checkpoint inhibitors or chemotherapy the effects increase(Djureinovic, Wang, & Kluger, 2021). There are promising results of APX005M for pancreatic adenocarcinomas(O'Hara et al., 2021). There are phase I clinical trials of LVGN7409 (NCT05075993) and CDX-1140 (NCT03329950) for gastric cancer to evaluate safety and tolerability as well immunologic effects, as well as Phase II clinical study of APX005M combined with chemoradiation for gastric and GEJ cancer (NCT03165994).

Zolbetuximab (IMAB362) are targeting Claudin18.2 (*CLDN18.2*), which are usually incorporated in gastric mucosa epithelial tight junctions. When gastric epithelial cells modify into cancer cells Claudin18.2 becomes revealed and represents a very distinct target for therapies. A randomized phase II study of zolbetuximab in combination with the chemotherapy regimen EOX analyzed for a first line therapy for advanced gastric and GEJ adenocarcinoma which expressed CLDN18.2 in 40& or more of their tumor cells. Adding zolbetuximab to chemotherapy lead to longer progression free survival (HR=0.44%; 95%CI, 0.29-0.67; p<0.0005) and overall survival (HR=0.55; 95%CI, 0.39-0.77; p,0.0005). There are currently two phase III clinical trials active. The first is a global, double-blind, randomized study of the

efficacy of zolbetuximab in combination with CAPOX compared to a placebo and CAPOX for locally advanced unresectable or metastatic G/GEJ adenocarcinoma which are positive for Claudin 18.2 and HER-2 negative (NCT03653507) called GLOW trial. The other phase III clinical trial is also a global, double-blind, randomized trial of Zolbetuximab but with mFOLFOX regimen instead of CAPOX for the same status of G/GEJ adenocarcinoma (NCT03504397).

MCS110 targets the colony stimulating factor 1 (*CSF-1*). Blocking CSF-1 is associated with an improved response to chemotherapy or immune checkpoint inhibitor and is related to as a stimulant for cancer therapies. There is a single arm open label phase II study combining the PD-1 inhibitor PDR001 with MCS110 for patients with gastric cancer. However, this study has not released any results yet, but was expected to be finished in December 2019.

Tremelimumab is a humanized monoclonal antibody against CTLA-4 and is normally investigated together with durvalumab, a PD-L1 antibody. Together they were thought to be a great step forward in immunotherapy but haven't been established in clinical practice(De Mello, Lordick, Muro, & Janjigian, 2019). Currently there is the PRODIGE 59-DURIGAST trial, a randomized, phase II trial assessing the safety and efficacy of either durvalumab plus the FOLFORI regimen or duvalumab with FOLFORI and tremelilumab for advanced G/GEJ adenocarcinoma(Evrard et al., 2021) and the INFINITY phase II study of a tremelilumab and durvalumab combination for a non-surgical management of microsatellite highly instable G/GEJ(Raimondi et al., 2021).

In contrast, ipilimumab (IgG1) is a clinically established CTLA-4 inhibitor with multiple successful approvals (e.g., melanoma) and stronger Fc-mediated effector function compared with tremelimumab (IgG2). From a translational perspective, future gastric cancer studies that pursue CTLA-4 blockade may therefore preferentially consider ipilimumab or next-generation CTLA-4 antibodies, provided an appropriate safety strategy and biomarker rationale.

Catumaxomab is a bispecific antibody against the epithelial cell-adhesion molecule (EPCAM) and CD3, expressed on certain T-Cells. It was developed for treatment of a malignant ascites as results of different cancer entities in addition to chemotherapy. In a randomized phase II clinical trial no significant improvements were accomplished administering catumaxomab additionally to chemotherapy, but an administrable safety profile was indicated (Knödler et al., 2018). There is an open label, randomized, controlled phase III trial on its way investigating catumaxomab on patients with recurrent or metastatic gastric cancer with peritoneal metastasis (NCT04222114).

Epacadostat inhibits indoleamine 2,3-dioxygenase-1 (IDO1), which is released by tumor cells to decrease antitumor activity of T-cells. Epacadostat has been investigated in many different trials for various cancer entities to support especially PD-1 inhibition. No successful long-term benefit has been shown however and also the latest results of a randomized phase III clinical trial for metastatic melanoma, the ECHO-301/KEYNOTE-252 trial were not showing an

improvement of OS or PFS(Long et al., 2019). Three trials included patients with gastric adenocarcinoma, but no results have been published (NCT03196232, NCT03196232) and one trial was terminated (NCT03277352).

NGM707 is a dual antagonist monoclonal antibody directed against immunoglobulin like transcript 2 (ILT2 or *LILRB1*) and immunoglobulin like transcript 4 (ILT4 or *LILRB2*), which are upregulated in patients that show little to no response to immune checkpoint inhibition(Mondal et al., 2021). There is one phase I clinical trial assessing the safety and efficacy of NGM707 in combination with pembrolizumab in advanced and metastatic solid cancers including gastric cancer (NCT04913337, expected end date July 20225).

The novel immunotherapeutic **PRL3-ZUMAB** attaches to the oncogenic phosphatase of regenerating liver 3 (PRL3 or *PTP4A3*), which is overexpressed in various types of tumors but not in normal tissue. PRL3-ZUMAB binds to PRL3 and then engages macrophages, natural killer cells and B cells(Thura et al., 2019). Currently there is an open label, single dose phase II clinical trial assessing the monoclonal antibody as a monotherapy for solid tumors like gastric cancer and hepatocellular cancer with a PRL-3 expression (NCT04118114).

INBRX-105 is bispecific antibody targeting PD-L1 and as a agonist the human 4-1BB receptor. 4-1BB can modify various immunoregulating factors like activation of B cells, natural killer cells, dendritic cells, CD4 t cells and others. A first phase I clinical trial of INBRX-105 combined with pembrolizumab in patients with solid tumors including gastric adenocarcinoma is on its way (NCT03809624, estimated end date December 2023).

Ceralasertib (AZD6738) and **Elimusertib** (BAY 1895344) are oral inhibitors of the ataxia telangiectasia and Rad3-related (ATR)-specific kinase, which blocks the activation of DNA damage repair and instigates apoptosis in ATR-overexpressing tumor cells and thereby boosting immunotherapy. Ceralasertib demonstrated encouraging anti-tumor potency and a safety study in phase II clinical trial combined with durvalumab in advanced gastric cancer(Kwon et al., 2022). Momentarily there are two active studies, a phase I trial assessing the synergy of DS-8201a and ceralasertiv in advanced HER-2 positive solid tumors (NCT04704661) and a phase I/II trial investigating ceralasertiv with chemotherapy, durvalumab or Olaparib in advanced solid malignancies including gastric, breast and ovarian cancer (NCT02264678). Elimusertib was inly tested in preclinical settings with restricted efficacies due to lack of absorption in cancer tissue but is currently investigated in two phase I trials with either FOLFOX (NCT04535401) or cisplatin(/gemcitabine) (NCT04491942) chemotherapy in advanced solid tumors.

4.3.4 Signal transduction inhibitors

Signal transduction inhibitors are substances that prevent signaling between two different molecules inside a cell. Interrupting cell signaling can lead to various consequences for a cell

from malfunctioning of key processes or a disrupted cell division to the death of a cancer cell. Different signal transduction inhibitors are being researched for the treatment of cancer.

Signal transduction inhibitors			
41	capivasertib	AKT1,AKT2,AKT3	Signal transduction inhibitors
42	MK 2206	AKT1,AKT2,AKT3	Signal transduction inhibitors
43	ONC 201	AKT1,AKT2,AKT3,MAPK1	Signal transduction inhibitors
44	Dalpiciclib	CDK4,CDK6	Signal transduction inhibitors
45	Silmitasertib	CSNK2A1	Signal transduction inhibitors
46	GC1118	EGFR	Signal transduction inhibitors
47	Nimotuzumab	EGFR	Signal transduction inhibitors
48	Poziotinib	EGFR,ERBB2	Signal transduction inhibitors
49	Pyrotinib	EGFR,ERBB2	Signal transduction inhibitors
50	Varlitinib	EGFR,ERBB2	Signal transduction inhibitors
51	MCLA-129	EGFR,MET	Signal transduction inhibitors
52	[131I]-SGMIB Anti-HER2 VHH1	ERBB2	Signal transduction inhibitors
53	anbenitamab	ERBB2	Signal transduction inhibitors
54	ARX788	ERBB2	Signal transduction inhibitors
55	BAT 8001	ERBB2	Signal transduction inhibitors
56	cinrebafusp alfa	ERBB2	Signal transduction inhibitors
57	Disitamab vedotin	ERBB2	Signal transduction inhibitors
58	DP303c	ERBB2	Signal transduction inhibitors
59	GQ 1001	ERBB2	Signal transduction inhibitors
60	HLX22	ERBB2	Signal transduction inhibitors
61	MEDI4276	ERBB2	Signal transduction inhibitors
62	MRG002	ERBB2	Signal transduction inhibitors
63	SHR-A1811	ERBB2	Signal transduction inhibitors
64	XMT-1522	ERBB2	Signal transduction inhibitors
65	Sapitinib	ERBB2,ERBB3	Signal transduction inhibitors
66	Zenocutuzumab	ERBB2,ERBB3	Signal transduction inhibitors
67	Zanidatamab	ERBB2,SEM1	Signal transduction inhibitors
68	AMG 337	MET	Signal transduction inhibitors
69	Savolitinib	MET	Signal transduction inhibitors
70	VMD-928	NTRK1	Signal transduction inhibitors
71	Vactosertib	TGFBR1	Signal transduction inhibitors
72	vistusertib	MTOR	Apoptosis inducer
73	AZD8186	PIK3CB	Apoptosis inducer
74	GSK2636771	PIK3CB	Apoptosis inducer
75	Sitravatinib	EPHB1,AXL,MET,MERTK,MST1R, KDR,FLT1,FLT4	tumormicroenvironment

76	Masitinib	KIT,PDGFR,FGFR3,FYN,CSF1R,LYN,PTK2	tumormicroenvironment
77	dovitinib	KIT,PDGFRA,FLT3,KDR,FGFR3,FLT1,FLT4	tumormicroenvironment

Capivasertib (AZD5363), **MK 2206** and **ONC 201** all target the protein kinase B (PKB) or also know better known as Akt, which is a collective of three serine/threonine-specific protein kinases (AKT1, AKT2, and AKT3) which influence various major cellular processes like apoptosis, cell proliferation, cell migration or the glucose metabolism. Although AKT inhibitors have joined the clinical phases there is still restricted success due to numerous pathways that are able to take over for AKT. Ceritinib might help improve the efficacy of AKT inhibitors but is has only been investigated in cell lines so far(J. Wang et al., 2021). There is a one completed phase II study of capivasertib with paclitaxel for advanced gastric adenocarcinoma with PIK3CA mutation or amplification with nor results published (NCT02451956) and one phase II study hat was terminated (NCT02449655). There is also one completed phase II study investigating **MK2206**, which was completed with insufficient results reported (NCT01260701) and a phase I study terminated (NCT01705340) as well as terminated phase I/II clinical study researching ONC201 (NCT02420795). Right now, there is one phase II MATCH clinical study recruiting that intends to test the participants for genetic abnormalities and identify potential beneficiary treatments for a better planned treatment. Among others capivasertib is included as a treatment option in this study (NCT02465060).

Dalpiciclib (SHR6390) is an inhibitor for the cyclin-dependent kinase 4 and 6 (CDK4/6) which are responsible for the phosphorylation of downstream proteins and a promotion of cell proliferation. Dalpiciclib has shown potential in combination with pyrotinib especially in patients with HER-2 positive breast cancer(Y. Wang et al., 2021). A phase I clinical study of dalpiciclib with pyrotinib in patients with HER-2 positive gastric cancer has not published results (NCT03480256).

Silmitasertib (CX-4945) promotes apoptosis and generates autophagy by targeting casein kinase II (CK2 or *CSNK2A1*), which is amplified in various tumor cells. The activation of CK2 is also related to a higher resistance to chemotherapy. A study of silmitasertib combined with chemotherapy in cell lines and xenograft models shows potential of overcoming this resistance(M. Jung et al., 2019). A clinical phase I trial started in 2011 for advanced solid tumors has not published results and might have been terminated (NCT00891280). Right now there are no clinical trials for silmitasertib including gastric cancer, but for basal cell carcinoma (NCT03897036), medulloblastoma in children (NCT03904862) and to treat for the coronavirus (NCT04668209).

i. EGFR targeting therapies

The epidermal growth factor receptor (EGFR) is widely (over-)expressed for various cancer entities, especially in lung cancer. It is a transmembrane receptor, which is followed by a pathway that has major impact on numerous cell functions, carcinogenesis and cancer cell survival. In gastric cancer up to 30% of patients display EGFR mutations or amplifications and these are related to a poor prognosis(Kim et al., 2008). The typical EGFR inhibitors however have been unsuccessful in enhancing the overall survival of patients with gastric cancer when applied with chemotherapy in contrast to standard treatment alone(Lordick et al., 2013; Waddell et al., 2013). The following targeted therapies are novel EGFR inhibitors in trials for gastric cancer: **GC1118** is an anti-EGFR antibody displayed promising results in gastric cell lines independent of their KRAS mutation(J. E. Park et al., 2019) and in a phase I clinical trial for advanced solid tumors including gastric cancer(Oh et al., 2019). There were four randomized trials with control groups concerning the efficacy of **Nimotuzumab** between 2011 and 2015, which according to a meta-analysis have not shown any significant benefits for including to the EGFR inhibitor to a neoadjuvant setting with chemotherapy. The future role of Nimotuzumab stays uncertain with controversial results(Cao et al., 2021). **Poziotinib** (HM781-36B) is an irreversible pan-epidermal growth factor receptor inhibitor, blocking EGFR, ERBB2, ERBB4 and EGFR mutants. It is mainly investigated for lung cancer but was assessed for gastric cancer in a phase I/II clinical trial combined with paclitaxel and trastuzumab on Her-2 positive advanced GC (NCT017467710). It showed promising results but follow up trials have not been initiated so far(T. M. Kim et al., 2018). The dual kinase inhibitor (EGFR, ERBB2) **pyrotinib** is mainly researched for HER2 positive lung and breast cancer and was investigated in patients with gastric cancer in two phase I clinical trials with an unknown status and nor results published (NCT03480256, NCT02378389). Currently there are three active trials assessing pyrotinib combined with camrelizumab and chemotherapy in HER-2 positive gastric cancer (NCT05111444, NCT05070598) or by itself to analyze its safety (NCT02500199). **Varlitinib** (ASLAN001) is a reversible inhibitor of EGFR and ERBB2 mainly studied in breast cancer. A phase Ib clinical trial on advanced solid tumors including gastric cancer showed manageable safety profile with trastuzumab and paclitaxel(M. X. Lee et al., 2022). Presently there is one double-blind, randomized, placebo-controlled pahse II/III stufy evaluating varlitinib with mFOLFOX6 on EGFR/HER2 positive advanced or metastatic GC awaiting results (NCT03130790). There is another trial in Korea which is an open label, single-arm phase I/II study exploring varlitinib with paclitaxel on EGFR/HER2 comutated, advanced or metastatic GC (NCT05400915). The novel anti-EGFR and anti-c-MET bispecific antibody **MCLA-129** is undergoing its first trial in a phase I/II study assessing advanced solid tumors including NSCLSC and gastric cancer (NCT04868877).

ii. HER-2 targeting therapeutics

One of the four subtypes of gastric cancer is the subgroup of overexpressing human epidermal growth factor 2 (HER2 or *ERBB2*), which makes it one of the most promising and researched targets in the last decades of gastric cancer. Trastuzumab is the only FDA approved targeted therapeutic in advanced HER-2 positive GC, but is struggling with abti-HER2 drug resistance, Therefore the development of novel treatment options is still one of the main concerns in research for GC(Roviello et al., 2022). The following treatment options targeting ERBB2 are currently in clinical trials and have not yet been approved by the FDA. **[131I]-SGMIB Anti-HER2 VHH1** is a targeted radionuclide theranostic agent which consists of an antibody connected to a ^{131}I by a linker if N-succinimidyl 4-guanidino-methyl-3-iodobenzoate (SGMIB). A phase I trial demonstrated no adverse events in patients with breast cancer, which could make it a therapeutic alternative after unsuccessful anti-HER-2 therapies like trastuzumab due to its different therapeutic approach(D'Huyvetter et al., 2021). Currently there is one Phase II trial assessing VHH1 and its uptake in other cancer entities than breast cancer with HER-2 overexpression (NCT03924466).

Anbenitamab (KN026) is bispecific novel antibody which links to two specific HER2 epitopes and thereby shows a new approach to HER-2 therapeutics. A first phase I study assessed the safety profile of KN026 in patients with HER-2 positive metastatic breast cancer and demonstrated a well tolerable and promising efficacy with an ORR of 28.1% and a PFS of 6.8 months (95%CI, 4.2-8.3). A promising biomarker for anticipating an improved response was the co-amplification of CDK12(J. Zhang et al., 2022). There are currently four active trials investigating KN026 in gastric cancer, two of them phase I clinical studies evaluating the safety and tolerability (NCT03619681, NCT03847168). Additionally, there is one phase II trial assessing efficacy and safety in G/GEJ (NCT03925974) and one randomized, double-blind phase II/III trial researching KN026 in combination with chemotherapy consisting of paclitaxel, docetaxel and irinotecan, as a second line treatment for HER-2 positive advanced or metastatic gastric cancer (NCT05427383).

ARX788 is a first-generation antibody drug conjugate (ADC) which are known to create benefits in clinical settings and have small therapeutic windows due to toxicity to non-cancer cells. ARX788 displayed promising results in precilincal testing of xenografts of patients with breast and gastric cancer(Skidmore et al., 2020). Momentarily there is one phase I study investigating ARX768 in advanced solid tumors including gastric cancer with HER-2 overexpression in a dose escalation trial (NCT03255070).

BAT8001 is another novel ADC targeting HER-2 consisting of a trastuzumab biosimilar connected to a drug-linker batansine. It was investigated in an open label, dose escalation phase I trial in HER-2 positive breast cancer indicating an approving safety profile and encouraging efficacy(Agrawal et al., 2014). Currently there is a phase I clinical trial evaluating

safety, tolerability and pharmacokinetics for HER-2 positive solid tumors including G/GEJ adenocarcinoma (NCT04189211).

The bivalent, bispecific fusion protein **cinrebafusp alfa** (PRS-343) composed of an anti-HER2 antibody connected to a CD137 targeting anticalin. PRS-343 bridges CD137 positive T-cells with HER2 positive cancer cells causing mobilization of antigen specific cytotoxic t-lymphocytes(Hinner et al., 2019; Morales-Kastresana et al., 2022). A phase I clinical study was initiated to investigate cinrebafusp alfa with ramucirumab and paclitaxel in HER-2 positive G/GEJ (NCT05190445).

Disitamab vedotin (RC48) is a bispecific humanized novel HER-2 antibody linked to Monomethyl auristatin E (MMAE), a synthetic antineoplastic agent, with a cleavable linker. In a first phase I trial on HER-2 overexpressing locally advanced or metastatic solid cancer with a focus on gastric cancer(Y. Xu et al., 2021) RC48 displayed a high tolerability and encouraging anti-tumor efficacy. Momentarily there are two phase II clinical trials assessing RC48 for gastric cancer, one investigating RC48 combined with PD-1 inhibitor and neoadjuvant chemotherapy for locally advanced GC (NCT05113459) and one combining RC48, AK105 and cisplatin in advanced GC (NCT05313906).

The ADC **DP303c** conjugated of a HER-2 antibody and an undisclosed cytotoxic agent with no preclinical or clinical results published. Momentarily there is one open label phase II on unresectable locally advanced, recurrent or metastatic GC with positive HER-2 expression (NCT04826107).

Another ACD on HER-2 is **GQ1001** consisting of trastuzumab (HER-2 monoclonal antibody), a non-cleavable linker and as a cytotoxic payload composed of the microtubule-depolymerizing maytansinoid derivative (DM1)(Yu, Fang, Yun, Liu, & Cai, 2022). There are no results available yet, but there a dose-escalation phase I clinical trial assessing the safety of GQ1011 on HER-2 positive breast and gastric cancer (NCT04450732).

HLX22 is a humanized Ig G1 targeting HER-2 with a potential immune modulating activity causing in a cytotoxic T-lymphocyte response. There are no results yet published but a phase I clinical trial on advanced solid tumor overexpressing HER2 was just recently completed (NCT03916094). Additionally, there is a double-blind phase II study on HER2 positive locally advanced or metastatic GC as a first line therapy in combination with trastuzumab, oxaliplatin and capecitabine (NCT04908813).

The ADC **MEDI4276** composed of a biparatopic antibody binding to two nonoverlapping epitopes loaded with a tubulysin-based microtubule inhibitor. A phase I clinical trial HER2 expressing breast and gastric cancers displayed a promising anti-tumor activity, but a non-tolerable toxic profile at higher doses(Pegram et al., 2021). Since then, no other clinical trials investigating MEDI4276 were initiated.

MRG002 is a ADC composed of a monoclonal antibody biosimilar to trastuzumab with a linker connecting to the cytotoxic agent MMAE(H. Li et al., 2021). A preclinical evaluation demonstrated a manageable toxicity profile and encouraging antitumor response. A phase I/II clinical trial on HER-2 positive advanced solid tumors and locally advanced or metastatic G/GEJ cancer (NCT04492488) and an open label phase II with the same inclusion criteria (NCT05141747).

SHR-A1811 is another ADC consisting of a HER2 antibody and a not yet disclosed cytotoxic substance. There are no results reported yet, but a phase I study of SHR-A1811 on HER2 positive gastric and colorectal cancer (NCT04513223).

The ADC **XMT-1522** conjugated of an anti-HER2 antibody and a load of 12 auristatin F-hydroxypropylamide (AF-HPA moieties, which can inhibit tubulin polymerization. In xengraft models XMT-1552 showed high efficacy in HER-2 positive breast and gastric cancer(Le Joncour et al., 2019). A phase Ib dose escalation trial was completed in Janaury 2019 but has no results published yet (NCT02952729).

Sapitinib (AZD8931) is a novel inhibitor of EGFR, ERBB2 and ERBB3. In a phase I trial sapitinib combined with oxaliplatin and capecitabine chemotherapy in operable patients of esophagogastric andenocarcinoma and demonstrated an acceptable safety profile as well as (Thomas et al., 2020). Currently there are no trials assessing AZD8931 in gastric cancer, only in metastatic breast cancer (NCT02299999) and NSCLC (NCT02117167).

The bispecific monoclonal antibody (mAb) **zenocutuzumab** (MCLA-128) targets ERBB2 and ERRB3. It attempts to surpass the resistance of HER-2 targeted therapies. In a phase I/II clinical trial on various advanced malignancies zenocutuzumab demonstrated comparable distribution attributes to other therapeutics(de Vries Schultink et al., 2020). There are now phase I/II clinical trials under way which are evaluated on advanced solid tumors which are positive for neregulin-1 (NRG1) fusion (NCT04100694, NCT02912949).

Zanidatamab (ZW25) is a novel HER-2 targeting antibody which displayed first encouraging results in a phase I trial on breast cancer with an ORR of 46%("ZW25 Effective in HER2-Positive Cancers," 2019). Currently there are 4 clinical trials investigating ZW25 on gastric cancer. One active clinical phase I trial on advanced HER-2 expressing tumors (NCT02892123) in the U.S., two phase II clinical studies assessing zanidatamab with tislelizumab as a second line in advanced HER-2 positive gastric cancer (NCT05270889) and combined with chemotherapy on gastrointestinal tumors like gastric cancer or colorectal cancer (NCT03929666), and one open label phase III study called HERIZON-GEA-01 with various cohorts evaluating ZW25 in combination with chemohtherapy with and without tislelizumab in Patients With HER2-positive Advanced or Metastatic Gastric and Esophageal Cancers (NCT05152147).

iii. Other signal transduction inhibitors

AMG 337 is a small molecule *MET*-inhibitor that is assessed for numerous cancer entities. A *MET* amplification is related to a poor prognosis in gastric and GEJ adenocarcinoma. A phase II clinical trial on patients with gastric, GEJ and esophageal cancers with *MET* amplification displayed promising results on anti-tumor activity with an ORR of 18% in the cohort of G/GEJ/E(Van Cutsem et al., 2019). Momentarily there are no clinical trials ongoing with 2 terminated (NCT02344810, NCT02016534).

The *MET*-inhibitor **savolitinib** (volitinib, AZD6094) was recently approved in China for metastatic NSCLC with MET exon 14-skipping alterations in patients who are unsuitable for a progression of chemotherapy(Markham, 2021). Although three studies on patients with advanced gastric adenocarcinoma were completed in South Korea (NCT02449551, NCT02447406, NCT02447380) no results were internationally reported. Accordingly, there are only results on the latest trials investigating advanced papillary renal cell carcinoma with improved survival rates (Pal et al., 2021) and on EGFR and MET positive NSCLC with promising results(Sequist et al., 2020). In gastric cancer savolitinib is still being investigated in a single arm, open label phase II clinical trial in locally advanced or metastatic GC or GEJ adenocarcinoma with MET amplifications in China.

The oral small molecule inhibitor **VMD-928** targets tropomyosin receptor kinase A (TrkA or *NTRK1*) and irreversibly attaches two TrkA together. NRTK1 gene fusions or an amplification of TrkA induce oncogenic pathways in various cancer entities. First results of a phase I trial on numerous cancer types with TrkA overexpression demonstrated a good safet profile and identified different tumors with a high number of TrkA amplification like thymic carcinomas and mesotheliomas, but not yet in gastric cancer(Chung et al., 2021). Further investigations are expected.

The inhibitor **vactosertib** (TEW-7197) of the serine/threonine kinase transforming growth factor (TGF)-beta receptor type 1 (*TGFBR1*) blocks its related signaling and thereby restrains cancer proliferation(Yoon et al., 2020). A dose escalation phase I clinical trial demonstrated manageable pharmacokinetics and good safety profile leading to the initiation of further clinical studies(S. Y. Jung et al., 2020). TEW-7197 is investigated in two phase I/II trials, one in combination with pemrolizumab in patients with metastatic colorectal or gastric cancer (NCT03724851) and one combined with paclitaxel in metastatic gastric cancer (NCT03698825). Additionally, vactosertib is evaluated in gastric cancer in phase II clinical trials either with durvalumab (NCT04893252) or as a second-line treatment with paclitaxel and ramucirumab (NCT04656002).

Vistusertib (AZD2014) is an inhibitor of the mammalian target of rapamycin (mTOR) which induces apoptosis in addition to being a signal transduction inhibitor. Vistusertib failed to show any significant advantages in various cancer entities for example in B-cell malignancies (Collins et al., 2021; Eyre et al., 2019). Three phase II clinical trials on gastric cancer in South

Korea were terminated before completion with no results published (NCT03082833, NCT03061708, NCT02449655).

AZD8186 is a selective inhibitor of beta isoform of phosphoinositide-3 kinase (PI3Kβ or *PI3KCB*) leading to a decrease of tumor proliferation by blocking the PI3K/Akt/mTOR signaling pathway. A first phase I clinical trial confirmed an adequate safety profile and showed initiatory anti-tumor activity(Choudhury et al., 2022). Momentarily there are two phase I/II clinical trials evaluating AZD8186 in GC in combination with paclitaxel in South Korea (NCT04001569, NCT04526470).

Another inhibitor of PI3Kβ is **GSK2636771**, which displayed tolerable safety profile among advanced solid tumors(Mateo et al., 2017) and in combination with enzalutamide in metastatic castration resistant prostate cancer with restricted anti-tumor activity(Sarker et al., 2021). A phase I/II clinical trial of GSK2636771 in gastric adenocarcinoma was recently completed with no results reported yet (NCT02615730). GSK2636771 is also part of the MATCH screening trial already mentioned at capivasertib (NCT02465060).

Sitravatinib (MGCD516) is an inhibitor of multiple receptor tyrosine kinases including the hepatocyte growth factor receptor (HGFR; c-Met; *MET*), vascular endothelial growth factor 1 (*FLT1*)/2 (*KDR*)/ 3 (*FLT4*), tyrosine-protein kinase receptor UFO (*AXL*), mast/stem cell growth factor receptor (SCFR or *KIT*), the receptor tyrosine kinase MER (*MERTK*), discoidin domain receptor 2 (*DDR2*), members of the PDGFR family, *RET* (rearranged during transfection), tropomyosin-related kinases (*TRK*) and members of the ephrin (Eph) family of receptor tyrosine kinases (including Eph receptor B1 or *EPHB1*). In a first I/Ib trial MGCD516 showed moderate activity against tumor tissue and a tolerable safety profile in advanced solid tumors(Bauer et al., 2022). A phase I/II study is currently investigating sitravatinib either as monotherapy or combined with tislelizumab in patients with advanced or metastatic HCC or G/GEJ adenocarcinoma (NCT03941873).

Masitinib is an oral inhibitor of the wildtype and mutant form of KIT, including Exons 9 and 11. It also blocks other tyrosine kinases inhibitors like PDGFR or fibroblast growth factor receptor 3 (FGFR3). In a randomized, open-label phase II clinical trial assessing the safety and efficacy of masitinib in advanced gastro-intestinal tumors (GIST) displayed an improved progression free survival if masitinib is followed by standard of care in 2014(Adenis et al., 2014). Further trials were initiated of which two phase II clinical trials were completed with no results published (NCT00998751, NCT01506336) and two phase III clinical studies were terminated (NCT00812240, NCT02009423).

The oral inhibitor **Dovitinib** (TKI258) selectively binds to FGFR3 resulting in a suppression of tumor proliferation. Moreover, TKI258 interferes with KIT, PDGFRA, FLT3, KDR, FLT1, and FLT4. There were three clinical studies completed investigating TKI258 in gastric cancer, one phase I/II with FGFR2 amplification in Korea(NCT01719549), two phase II clinical trials

assessing TKI258 with docetaxel (NCT01921673) and in a dose escalation trial (NCT01576380), but no results were reported internationally. Two preclinical studies demonstrated to reduce resistance to trastuzumab in cell lines of patients with gastric cancer(Piro et al., 2016) and increase effectiveness of chemotherapy in gastric cancer(Crawford et al., 2021). No trials are currently assessing dovitinib in gastric cancer.

4.3.5 Toxic delivering molecules

Toxic delivering molecules are intended to decrease side effects by administering toxic therapeutics directly to tumor cells and releasing them into cancer cells only(Kundu, Das, & Chattopadhyay, 2019).

Toxic delivering molecules			
92	SKB-264	TACSTD2	Toxin delivering molecules

The antibody drug conjugate SKB-264 targets trophoblast antigen 2 (TROP2 or *TACSTD2*) and is connected to a cytotoxic, belotecan-derived payload. TROP2 is a glycoprotein which is amplified in numerous solid tumors and manages tumor proliferation and invasion(Goldenberg, Stein, & Sharkey, 2018). A first trial in humans for SKB-264 locally advanced unresectable/metastatic but refractory solid tumors was initiated investigating gastric adenocarcinoma among others solid tumors(Liu et al., 2020) (NCT04152499). There three additional trials not yet recruiting in China, two phase II clinical studies assessing NSCLC (NCT05351788) and triple-negative breast cancer (NCT05445908) and another phase III trial on triple-negative breast cancer (NCT05347134).

4.3.6 Tumor microenvironment

Tumors manage their environment according to their requirements. A variety of cell types are associated with changes in the microenvironment including fibroblasts, nerves, vascular endothelial and inflammatory cells. These cells are able to release cytokines, chemokines and other molecules instigating tumor growth and invasion(Oya, Hayakawa, & Koike, 2020).

Tumormicroenvironment			
78	BL-8040	CXCR4	Tumormicroenvironment
79	AZD4547	FGFR1,FGFR2,FGFR3	Tumormicroenvironment
80	derazantinib	FGFR1,FGFR2,FGFR3	Tumormicroenvironment
81	CPL304110	FGFR1,FGFR2,FGFR3,FGFR4	Tumormicroenvironment
82	Futibatinib	FGFR1,FGFR2,FGFR3,FGFR4	Tumormicroenvironment
83	ICP-192	FGFR1,FGFR2,FGFR3,FGFR4	Tumormicroenvironment
		FGFR1,FGFR2,FGFR3,FGFR4,KIT,PD	
84	Catequentinib	GFRA,PDGFRB,RET,KDR,FLT4	Tumormicroenvironment
85	Bemarituzumab	FGFR2	Tumormicroenvironment
86	RLY-4008	FGFR2	Tumormicroenvironment
87	AK-109	KDR	Tumormicroenvironment

88	Apatinib	KDR,FLT1,FLT4	Tumormicroenvironment
89	fruquintinib	KDR,FLT1,FLT4	Tumormicroenvironment
90	Crenolanib	PDGFRA,PDGFRB,FLT3	Tumormicroenvironment
91	Vorolanib	PDGFRA,PDGFRB,KDR,FLT1,FLT4	Tumormicroenvironment
91	TTI-101	STAT3	Tumormicroenvironment

BL-8040 is an inhibitor of CXCR4 which is regularly expressed in progenitor and hematopoietic stem cells, but its overexpression leads to resistance to chemotherapy of cytarabine in cancer tissues(Borthakur et al., 2021). BL-8040 is included in a phase I/II study that investigates multiple immunotherapies in advanced unresectable or metastatic G/GEJ adenocarcinoma investigating therapeutics like 5-fluorouracil, leucovorin, oxaliplatin and atezolizumab (NCT03281369).

All the fibroblast growth factor receptor (FGFR1, FGFR2, FGFR3, FGFR4) are influential on several cell functions and tissue homeostasis. The family of FGFRs are also involved in tumor microenvironment regulations like cell proliferation and invasion making it a target for therapeutics(Yashiro & Matsuoka, 2016). **AZD4547** is an inhibitor of the tyrosine kinases FGFR-1,2, and 3 and was assessed in a randomized phase II SHINE study in advanced gastric adenocarcinoma with FGFR2 amplification a second line treatment compared to paclitaxel. Although AZD4547 was well received it showed no improvement in PFS over paclitaxel(Van Cutsem et al., 2017). No current trials are known except for the MATCH trial (NCT02465060) which has already been mentioned. **Derazantinib** (ARQ 087) targets FGFR1-3 as well demonstrating sufficient anti-tumor activity in a phase II trial of in intrahepatic cholangiocarcinoma with FGFR2 mutations or amplifications(Javle et al., 2022). There is momentarily one phase I/II study of derazantinib either by itself or combined with ramucirumab, paclitaxel, atezolizumab in gastric adenocarcinoma (NCT04604132). **CPL304110** is an inhibitor of the whole FGFR family, binding to all four receptors (FGFR1-4). Because it displayed a advantageous pharmacokinetic profile as well as a manageable toxicity(Yamani et al., 2021), a first in human phase I trial was initiated in bladder, squamous cell lung and gastric cancer (NCT04149691). Another oral inhibitor of FGFR1-4 is futibatinib, which demonstrated initiatory encouraging responses in advanced malignancies and a favorable safety profile(Bahleda et al., 2020) as well as clinical efficacy in tumor with FGFR aberrations(Meric-Bernstam et al., 2022) resulting in a phase II/III study including gastric and GE cancer (NCT04189445). A different inhibitor of FGFR 1-4 is the orally available **ICP-192** which displayed anti-tumor activity in a preclinical study as well as in a phase I clinical trial in advanced solid tumors with FGFR alterations(Ye Guo et al., 2021). Additionally, it is investigated in two phase I/II trials in advanced solid tumors (NCT03758664, NCT04565275) and two phase II clinical studies assessing ICP-192 in bladder urothelial cancer (NCT04492293) and advanced solid malignancies with FGFR gene alterations

(NCT05372120). **Catequentinib/anlotinib** (TQB2450) inhibits FGFR 1-4 among others like PDGFRA and PDGFRB, KDR, FLT1, FLT4 and FGFR 1-4. Anlotinib was investigated in many various clinical studies. A study disclosed that anlotinib combined with PD-L1 inhibition is advantageous in the therapy if gastric cancer(Zheng et al., 2022)

There are numerous trials evaluating anlotinib in gastric cancer currently. Among these ongoing studies there is a randomized, open-label, controlled phase III trial with anlotinib in combination with AK105, paclitaxel and docetaxel in GC/GEJ adenocarcinoma. Additionally, there are various phase II studies assessing anlotinib with tislelizumab for immunotherapy in gastrointestinal cancers (NCT04777162), with toripalimab in advanced G/GEJ cancer as a first line therapy (NCT04278222), combined with TAS102 in refractory metastatic gastric cancer and with nivolumab in unresectable or metastatic GC and esophageal cancer after first line therapy (NCT04503967).

Bemarituzumab (FPA144) is a humanized antibody targeting FGFR2 which demonstrated manageable tolerability and an anti-tumor activity in advanced-stage gastroesophageal cancer as a monotherapy(D. V. T. Catenacci et al., 2020). There was a randomized, double-blind phase II trial recently completed awaiting results which evaluated FPA144 with FOLFOX6 in patients with advanced G/GEJ cancer (NCT03694522). Momentarily it is examined in a phase III trial in combination with chemotherapy with FGFR2b overexpression (NCT05052801). Furthermore, there are phase I studies inspecting bemarituzumab with chemotherapy and nivolumab (NCT05322577, NCT05111626) and as a monotherapy (NCT05325866). The other novel selective inhibitor of FGFR2 **RLY-4008** displayed encouraging first results for safety, tolerability and clinical anti-tumor activity in solid malignancies with FGFR2 alterations(Goyal et al., 2021). The first in human clinical trial is set to be completed in October 2024 (NCT04526106).

The monoclonal antibody **AK-109** targets the vascular endothelial growth factor 2 (VEGFR2 or *KDR*) and thereby reducing tumor angiogenesis and tumor cell proliferation. Momentarily there are three clinical trials assessing AK-109, two of them being phase I/II studies of AK-109 with AK-104 in advanced solid tumors (NCT05142423) and advanced G/GEJ adenocarcinoma (NCT04982276) and phase I dose escalation trial on solid tumors (NCT04547205).

The small molecule inhibitor of VEGFR-2, FLT1 and FLT4, the kinases of the vascular endothelial growth factor receptor, **Apatinib** (YN-968D1) has been thoroughly investigated in numerous trials but still are inconclusive concerning the combination of apatinib and S-1(C. Zhang, Yu, Zhang, & Liu, 2020). Currently there are 34 trials investigating apatinib in gastric cancer in China, where it was approved by the China National Food and Drug administration (CFDA) for the treatment of advanced gastric adenocarcinoma(Zhen et al., 2018). In the U.S. there are four active trials ongoing, of which none are examining gastric cancer (NCT03396211, NCT03764293, NCT04073615, NCT04119453). A phase I clinical trial

investigatet apatinib with pembrolizumab in previously treated advanced malignancies, which was terminated (NCT03407976). The other small molecule inhibitor **fruquintinib** targeting the same kinases of the VEGFR family, was also approved by the CFDA in 2018 for the treatment of metastatic colorectal cancer(Shirley, 2018). There are currently six clinical trials in China assessing fruquintinib in gastric cancer including a randomized, double-blind, placebo-controlled phase III study in combination with paclitaxel (NCT03223376). In the U.S. there are currently no studies assessing fruquintinib in gastric cancer, but metastatic colorectal cancer (NCT05368805, NCT04322539, NCT03251378) and other cancer entities. The treatment of advanced gastric cancer with fruquintinib is still unsettled and especially in China under investigation.

Crenolanib (CP-868596) is a small molecule inhibitor of the platelet-derived growth factor receptor (PDGFR) A and B and the tyrosine kinase FMS-like tyrosine kinase 3 (FLT3). A trial of crenolanib investigating advanced esophagogastric adenocarcinoma as a second line therapy with a ramucirumab and paclitaxel but was terminated early due to a removal of crenolanib by the sponsor (Moy et al., 2022). Momentarily there are no further studies in gastric or gastroesophageal cancer, whereas there are mainly studies assessing acute myeloid leukemia. Furthermore **vorolanib** (CM082/X-82) is an inhibitor of PDGFR and VEGFR. A phase Ib clinical trial of vorolanib in combination with immune checkpoint inhibitors demonstrated encouraging results and controllable toxicity in gastrointestinal and lung cancer(Bagegni et al., 2022). Another phase I clinical trial assessing X-82 in combination with checkpoint inhibitors like nivolumab and pembrolizumab in solid tumors was terminated (NCT03511222). Momentarily there are two active trials, ne phase II clinical trial evaluating vorolanib extensive-stage small cell lung cancer (NCT04373369) and a phase III study in metastatic renal cell cancer combined with everolismus (NCT03095040).

TTI-101 is an inhibitor of signal transducer and activator of transcription 3 (STAT3) which is a factor in transcription and a major signaling element for tumor proliferation and invasion. The oral STAT3 inhibitor is evaluated in a phase I study of patients with advanced cancer like breast cancer, melanoma and gastric adenocarcinoma (Tsimberidou, Achaval, Alibhai, & Kaseb, 2021).

4.3.7 Others

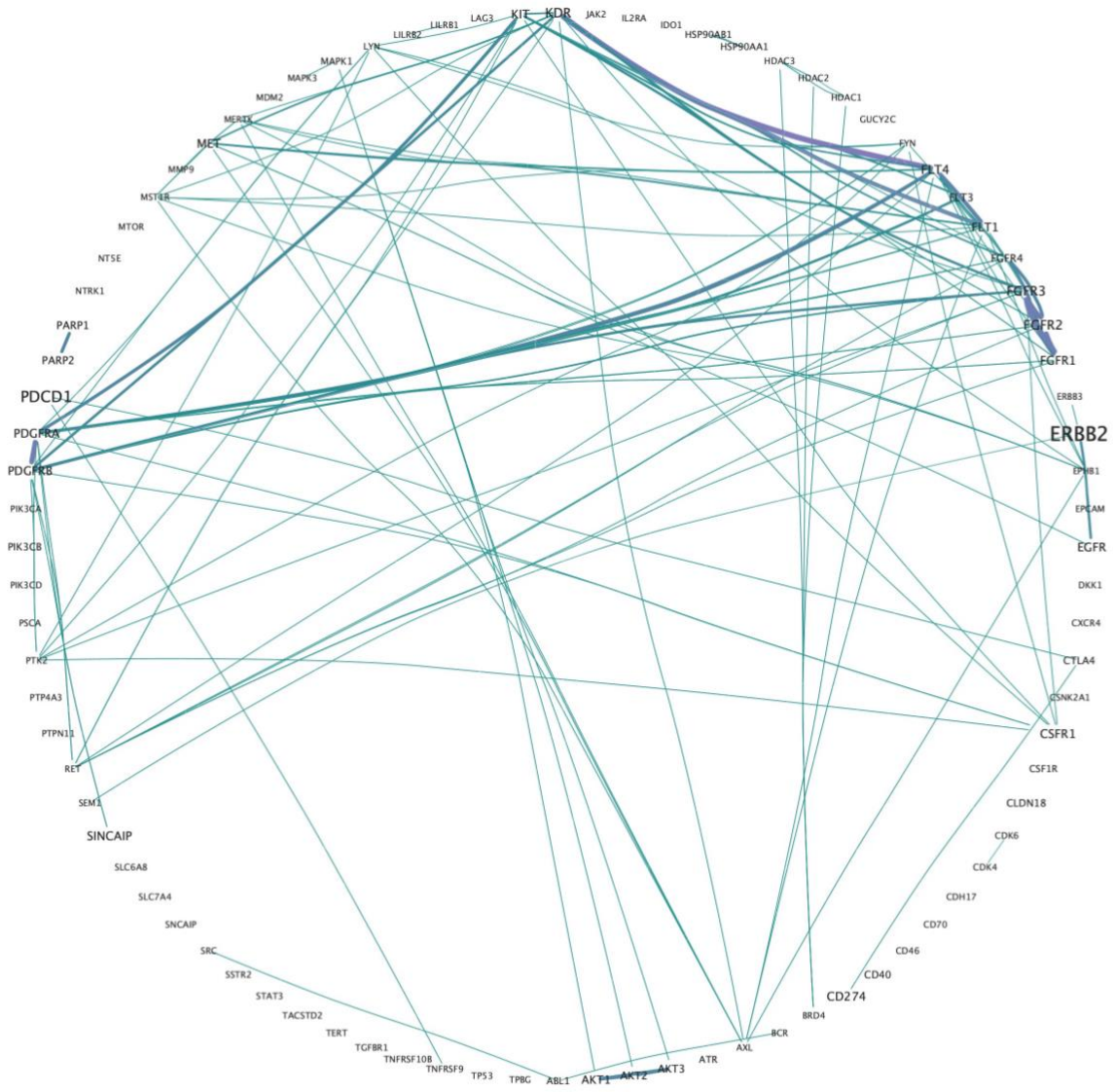
Other		
92	DKN-01	DKK1
93	Andecaliximab	MMP9

DKN-01 is an inhibitor of the Wnt signaling modulator dickkopf-1 (DKK1) which is regularly amplified in tumors and related to a poor prognosis. A first phase I trial for dose escalation demonstrated manageable tolerability as well as an increased anti-tumor activity in combination with PD-L1 inhibitors in advanced esophagogastric carcinoma(Klempner et al.,

2021). Currently, there is a study if DKN-01 with tislelizumab with or without chemotherapy in patients with G/GEJ adenocarcinoma as well as gastro-esophageal cancer (NCT04363801). The monoclonal antibody **andecaliximab** (ADX) targeting matrix metalloproteinase 9 (MMP9), which is associated with protumorigenic processes, and its reduction can decrease metastasis. First trials were showing anti-tumor activity, like a phase Ib in Japanese patients with G/GEJ adenocarcinoma in combination with anti-PD-1(A. K. Yoshikawa et al., 2022), a randomized, open-label phase II study of andecaliximab with nivolumab in comparison to nivolumab alone in advanced gastric cancer(M. H. Shah et al., 2017) or a phase Ib trial of ADX combined with S-1 and platinum gastric adenocarcinoma(Ooki et al., 2022).

4.3.8 Target gene combination

In total there were 93 targeted therapies interacting with 86 target genes including gastric cancer in their inclusion criteria since 1st of January 2015. Figure 13 shows the target genes in a circular diagram linking genes that were targeted by the same therapeutic. The table on the right side displays the genes in alphabetically order following the linked genes. ERBB2 was the main target gene (19) investigated followed by PD-L1 (16) and tumor microenvironment targets like FGFR (8) and KDR (6). The table additionally shows the genes which they are combined with and in brackets the number of their association.



Target gene	#	combined with (# of target therapies combining these two targets)
ERBB2	22	SEM1(1),ERBB3(1),EGFR(3)
ABL1	2	BCR(1)
AKT1	5	AKT2(4),AKT3(4),MAPK1(1)
AKT2	4	AKT1(4),AKT3(4),MAPK1(1)
AKT3	4	AKT1(4),AKT2(4),MAPK1(1)
ATR	2	
AXL	1	MET(1),MERTK(1),MST1R(1),KDR(1),FLT1(1),FLT4(1)
BCR	1	ABL1(1)
BRD4	1	HDAC1(1),HDAC2(1),HDAC3(1)
CD274	7	CTLA4(1)
CD40	3	
CD46	1	
CD70	1	
CDH17	1	
CDK4	1	CDK6(1)
CDK6	1	CDK4(1)
CLDN18	3	
CSF1R	2	LYN(1),PTK2(1),FGFR3(1),FYN(1),KIT(1),PDGFRA(1),PDGFRB(1)
CSNK2A1	1	
CTLA4	3	CD274(1),PDCD1(1)
CXCR4	1	
DKK1	1	
EGFR	7	ERBB2(3),MET(1)
EPCAM	1	
EPHB1	1	AXL(1),MET(1),MERTK(1),MSTR1(1),KDR(1),FLT1(1),FLT4(1)
ERBB3	1	ERBB2(1)
FGFR1	7	FGFR2(6),FGFR3(6),FGFR4(4),KIT(1),PDGFRA(1),PDGFRB(1),KDR(1),RET(1),FLT4(1)
FGFR2	9	FGFR1(6),FGFR3(6),FGFR4(4),KIT(3),PDGFRA(1),PDGFRB(1),KDR(1),RET(1),FLT4(1)
FGFR3	9	FGFR1(6),FGFR2(6),FGFR4(4),KIT(1),PDGFRA(3),PDGFRB(3),KDR(2),RET(1),FLT4(2),LT1(1),FN(1),CSFR1(1),LN(1),PTK2(1)
FGFR4	4	FGFR1(4),FGFR2(4),FGFR3(4),KIT(2),PDGFRA(1),PDGFRB(1),KDR(1),RET(1),FLT4(1)
FLT1	6	FLT4(5),AXL(1),EPHB1(1),FGFR3(1),KDR(5),MERTK(1),MET(1),MST1R(1),PDGFRA(1),PDGFRB(1)
FLT3	4	FLT4(1),KDR(2),KIT(2)MERTK(1),PDGFRA(3),PDGFRB(3)
FLT4	8	FLT3(5),FLT3(1),AXL(1),EPHB1(1),FFGFR1(1),FGFR2(1),FGFR3(1),FGFR4(1),KDR(7),KIT(2),MERTK(1),MET(2),MST1R(1),PDGFRA(4),PDGFRB(4),RET(1)
FYN	1	FGFR3(1),CSFR1(1),LYN(1),PTK2(1),KIT(1),PDGFRA(1),PDGFRB(1)
GUCY2C	1	
HDAC1	1	HDAC2(1),HDAC3(1),BRD4(1)
HDAC2	1	HDAC1(1),HDAC3(1),BRD4(1)
HDAC3	1	HDAC1(1),HDAC2(1),BRD4(1)
HSP90AA1	2	HSP90AB1(2)
HSP90AB1	2	HSP90AA1(2)
IDO1	1	
IL2RA	1	
JAK2	1	
KDR	9	AXL(1),EPHB1(1),FGFR1(1),FGFR2(1),FGFR3(2),FGFR4(1),FLT1(5),FLT3(2),FLT4(7),KIT(2),RET(1),MERTK(1),MET(1),MST1R(1)PDGFRA(6),PDGFRB(6)
KIT	6	FGFR1(1),FGFR2(1),FGFR3(3),FGFR4(2),PDGFRA(4),PDGFRB(3),RET(1),KDR(2),FLT3(2),FLT4829,FN(1),CSFR1(1),LYN(1),CSF1R(1),LYN(1),PTK2(1)
LAG3	1	
LILRB1	1	
LILRB2	1	
LYN	1	CSF1R(1),FGFR3(1),FYN(1),KIT(1),PTK2(1),PDGFRA(1),PDGFRB(1)
MAPK1	2	AKT1(1),AKT2(1),AKT3(1),MAPK3(1)
MAPK3	1	NAPK1(1)
MDM2	1	
MERTK	1	AXL(1),EPHB1(1),FLT1(1),FLT4(1),KDR(1),MST1R(1),MET(1)
MET	7	AXL(1),EGFR(1),EPHB1(1)FLT1(2),FLT4(2),KDR(2),MERTK(1),MST1R
MMP9	1	
MST1R	1	FLT1(1),FLT4(1),KDR(1),MERTK(1),MET(1),AXL(1),EPHB1(1)
MTOR	1	
NT5E	1	
NTRK1	1	
PARP1	4	PARP2(4)
PARP2	4	PARP1(4)
PDCD1	13	CTLA4(1),TNFRSF9(1)
PDGFRA	7	FGFR1(1),FGFR2(1),FGFR3(3),FGFR4(1),KIT(4),KDR(3),RET(1),FLT4(4),FLT3(3),FLT1(1),SINCAIP(1)FN(1),CSFR1(1),LYN(1),PTK2(1),PDGFRB(6)
PDGFRB	6	FGFR1(1),FGFR2(1),FGFR3(2),FGFR4(1),KIT(3),KDR(3),RET(1),FLT4(4),FLT3(2),FLT1(1),SINCAIP(1)FN(1),CSFR1(1),LYN(1),PTK2(1),PDGFRA(6)
PIK3CA	1	
PIK3CB	3	
PIK3CD	1	
PSCA	1	
PTK2	1	CSFR1(1),FGFR3(1),FYN(1),KIT(1),LYN(1),PDGFRA(1),PDGFRB(1)
PTP4A3	1	
PTPN11	1	
RET	1	FGFR1(1),FGFR2(1),FGFR3(1),FGFR4(1),FLT4(1),KDR(1),KIT(1),PDGFRA(1),PDGFRB(1)
SEM1	1	
SLC6A8	1	
SLC7A4	1	
SNCAIP	1	PDGFRA(1),PDGFRB(1)
SRC	1	
SSTR2	1	
STAT3	1	
TACSTD2	1	
TERT	1	
TGFBR1	1	
TNFRSF10B	1	
TNFRSF9	1	PDCD1(1)
TP53	1	
TPBG	1	

Edge Stroke Color (Unselected) Mapping

Figure 13 Target genes and their combinations in targeted therapies for gastric cancer currently in clinical trial

5 Discussion

Most patients with gastric cancer are still diagnosed at an advanced and unresectable stage, which establishes the necessity for effective therapeutic alternatives. At present, FDA-approved targeted and biomarker-selected therapies for gastric/gastroesophageal junction (G/GEJ) adenocarcinoma include: the ERBB2 (HER2) inhibitor trastuzumab in combination with chemotherapy for HER2-positive advanced disease; the VEGFR-2 inhibitor ramucirumab (as monotherapy or with paclitaxel) after progression on fluoropyrimidine- or platinum-containing chemotherapy; nivolumab plus chemotherapy as first-line therapy for advanced/metastatic gastric, GEJ, and esophageal adenocarcinoma in patients with tumor PD-L1-positive population; pembrolizumab in combination with trastuzumab and fluoropyrimidine- and platinum-containing chemotherapy as first-line treatment for locally advanced unresectable or metastatic HER2-positive gastric and GEJ adenocarcinoma (accelerated approval); fam-trastuzumab deruxtecan for trastuzumab-pretreated HER2-positive locally advanced or metastatic G/GEJ adenocarcinoma; and zolbetuximab in combination with chemotherapy for CLDN18.2-positive, HER2-negative, previously untreated locally advanced unresectable or metastatic G/GEJ adenocarcinoma. Pembrolizumab monotherapy is primarily applied in gastric cancer via tissue-agnostic indications (e.g., MSI-H/dMMR and TMB-high) rather than a standalone PD-L1 CPS≥1 gastric indication(Easaw et al., 2025; M. A. Shah et al., 2023).

Our analysis identified a total of 905 targeted therapies in clinical trials that are not yet FDA-approved with respectively 2433 clinical trials regarding gastric cancer. The 905 targeted therapies showed to target 320 different target genes or proteins.

5.1 Emerging therapies

Recent clinical trials investigating targeted therapies for gastric adenocarcinoma reveal a growing emphasis on novel agents focusing on new targets. This thesis identified multiple therapies currently in development that have not yet received FDA approval but demonstrate promising clinical potential and will discuss the most relevant emerging directions for gastric adenocarcinoma converge on next-generation HER2 strategies, expanded immuno-oncology combinations, the rapidly growing antibody-drug conjugate (ADC) pipeline, and biomarker-defined novel targets. By identifying and categorizing these investigational therapies across 2433 clinical trials, this thesis highlights key emerging targets such as CLDN18.2, FGFR2b, and MET. Importantly, several candidates are being evaluated not only in gastric cancer–specific protocols but also in biomarker-driven basket and platform trials that enroll patients across tumor types (including gastric cancer) based on shared molecular alterations, thereby accelerating signal detection for rare genomic events.

5.1.1 HER-2 targeting therapies

Trastuzumab was the first HER-2 targeting therapy, which was able to show a significant improvement of OS and PFS in patients with HER-2 positive gastric cancer(Bang et al., 2010). The establishment of a drug resistance is still the main issue for HER-2 targeting therapeutics, also for trastuzumab. There are different mechanisms of resistance like a HER-2 heterogeneity, modifications in the PI3K/Akt pathway or a MET amplification(Bass et al., 2014). To avoid drug resistance predominantly two mechanisms are being tested. On the one hand there is the attempt to support HER-2 therapies with immunotherapies, like the just currently approved combination of pembrolizumab and trastuzumab, to enhance outcome and prognosis. On the other hand, there is effort to develop novel therapeutics, mainly antibody drug conjugates which consists of a antibody binding to the target receptor overexpressed in gastric cancer, mostly HER-2 and a cytotoxic component which is released into only cancer cells when the ADC connects to the target cells(Roviello et al., 2022). After a significant improved PFS and OS in heavily pretreated patients with G/GEJ adenocarcinoma trastuzumab deruxtecan (DS-8201a) was approved for with trastuzumab pretreated locally advanced or metastatic G/GEJ HER-2 positive cancer(Elizabeth C. Smyth et al., 2020), are two HER2-directed agents: zanidatamab (ZW25), a bispecific antibody targeting two distinct HER2 epitopes, and margetuximab, an Fc-engineered monoclonal antibody designed to enhance immune-mediated cytotoxicity, among the most noteworthy. Both are under evaluation in advanced-phase trials as monotherapy or in combination with chemotherapy and immunotherapy, but both haven't been approved by the FDA yet for gastric cancer(D. V. Catenacci et al., 2021; "ZW25 Effective in HER2-Positive Cancers," 2019).

It will also be interesting to see if trastuzumab deruxtecan will be able to enhance prognosis and outcome in patients which were not pretreated with trastuzumab (NCT04379596, NCT04014075) or in a neoadjuvant setting (NCT05034887).

Additionally, new screening methods like circulating tumor cells or tumor DNA in bloods samples will simplify identifying suitable patients without the need for invasive procedures(Mencel, Slater, Cartwright, & Starling, 2022).

5.1.2 Immunotherapies

Various immunotherapies, especially immune checkpoint inhibitors, have recently shown strong potential in the treatment of advanced gastric cancer. The latest ASCO guidelines on immunotherapy and targeted therapy for advanced gastroesophageal cancer(M. A. Shah et al., 2023) state, that patients with HER2-negative adenocarcinoma of the stomach or gastroesophageal junction (GEJ) and a PD-L1 combined positive score (CPS) ≥5 are recommended to receive first-line therapy with nivolumab and chemotherapy. For HER2-

positive patients with unresectable or metastatic disease, a combination of chemotherapy, trastuzumab, and pembrolizumab is advised as the preferred first-line treatment.

These updated recommendations identify immunotherapy and the increased importance it has shown recently. However, one of the biggest and ongoing challenges is the high rate of resistance to immune checkpoint inhibitors. Therefore, some of the current clinical trials are focusing on reducing resistance, such as through the use of KN046, a bispecific antibody targeting both PD-L1 and CTLA-4. Other combination strategies under investigation include pairing PD-L1 blockade with additional immune targets like TGF-βRII (SHR-1701), CD27 (CDX-527), or CTLA-4 (KN046).

Additionally, new immunotherapies are being explored in combination with other targeted agents, such as TQB2450 (a PD-L1 inhibitor) combined with the VEGFR inhibitor anlotinib, or with chemotherapy regimens like Toripalimab paired with CapeOx, SOX, or FOLFOX, aiming to reduce immune resistance mechanisms in tumor cells.

And then there are agents such as sotigalimab (APX005M), CDX-1140, and LVGN7409 which are being investigated to support immunotherapy by modulating the tumor microenvironment and enhancing antitumor immune responses. Meanwhile, ceralasertib and elimusertib are being evaluated for their ability to enhance immunotherapy efficacy by inhibiting DNA damage repair mechanisms, thereby increasing tumor immunogenicity and promoting apoptosis(Kwon et al., 2022; Pusch et al., 2024). These studies are being followed with high anticipation.

In summary, immunotherapy offers multiple avenues for targeting both tumor cells directly and their surrounding microenvironment. As most of the early-phase trials are not focused on one cancer entity and therefore not only aimed for gastric cancer, patients with GC are increasingly being included in these trials. Immunotherapies appear to hold the most long-term promise for the development of effective new targeted treatments in gastric cancer.

5.1.3 Antibody drug conjugates

Antibody drug conjugates (ADCs) are seen as another one of the emerging and innovative targeted therapies. Mostly these are already existing therapeutics, some chemotherapeutics and well as different targeted therapies, supposed to affect only cancer tumor cells and thereby minimize side and toxic effects. ADCs have enhanced safety and prognosis in patients with advanced gastric cancer(Khongorzul, Ling, Khan, Ihsan, & Zhang, 2020). For gastric cancer at this point the majority of the drugs are targeting HER2. DS-8201a and RC48 have shown satisfying results and were approved in HER-2 positive patients with advanced gastric cancer(N. Wang et al., 2022). But there are also other targets like TACSTD2 (SKB-264) being investigated. More targets have shown promising efficacies in other cancer entities and might be options in the near future(Thomas, Teicher, & Hassan, 2016). Further investigation will most likely enhance, safety and efficacy of treating patients with AGC.

5.1.4 Novel targets

The analysis of the genome of gastric cancer patients have also provided new targets for the management and treatment of GC. Especially the tight junction protein claudin-18 isoform 2 (CLDN18.2) and the hippo pathway are the two most promising therapeutic targets.

Recently, the results of the pivotal Phase III SPOTLIGHT and GLOW trials have established proof-of-concept for CLDN18.2-directed therapy in advanced gastric/GEJ adenocarcinoma, and zolbetuximab has entered first-line practice for eligible CLDN18.2-positive, HER2-negative patients. In parallel, other CLDN18.2-directed modalities (e.g., ADCs and cellular therapies) are advancing in early-phase development, which may help address primary or acquired resistance to antibody therapy(Easaw et al., 2025; F. Zhang, Okazaki, Nakayama, & Shitara, 2026).

Among the emerging targeted therapies in gastric adenocarcinoma, two particularly promising agents are bemarituzumab and savolitinib, which focus on the FGFR2b and MET pathways, respectively(T. S. Lee et al., 2023; Wainberg et al., 2024). Bemarituzumab is a monoclonal antibody specifically targeting FGFR2b, a receptor overexpressed in a subset of gastric tumors. In the FIGHT trial (NCT03694522), bemarituzumab demonstrated clinical benefit when combined with chemotherapy in patients with high FGFR2b expression. This lead to improved progression-free and overall survival compared to chemotherapy alone(Wainberg et al., 2024). These results highlight FGFR2b as a clinically actionable biomarker and position bemarituzumab as a leading candidate for future integration into personalized treatment strategies for FGFR2b-positive gastric cancer.

Savolitinib, a selective MET inhibitor, has shown early signs of efficacy in patients with MET-amplified gastric cancer, a population limited targeted treatment options in the past. Preliminary data from early-phase trials suggest that savolitinib may offer meaningful disease control in patient with MET amplification, verifying to further investigate in larger, biomarker-enriched studies(T. S. Lee et al., 2023). Together, these agents reflect a shift toward precision oncology, where therapeutic decisions are increasingly guided by tumor and individual specific molecular features rather than histology alone.

Additionally, the hippo pathway, which plays a major role in the process of gastric carcinogenesis, is in the focus of various preclinical trials. Especially the protein/protein interactions and upregulation of YAP/TAZ-TEAD appears to be a reasonable but difficult target. New therapeutic options targeting TGF-b or WNT are involved in the hippo-caused development of gastric cancer(Seeneevassen, Dubus, Gronnier, & Varon, 2022). There are novel targeted therapies here like SHR-1701 targeting TGF-β II. There are various strategies being investigated, but there is still a diverse amount of uncertainty in the development of a sufficient novel therapeutic(Seeneevassen et al., 2022).

Table 11 FDA-Approved Targeted Therapies in Gastric/GEJ Adenocarcinoma (2024).

Therapy	Target	Indication	Approval Status
Trastuzumab	HER2	HER2-positive advanced G/GEJ cancer (1st line, with chemo)	FDA-approved
Ramucirumab	VEGFR-2	Progression after fluoropyrimidine/platinum chemotherapy	FDA-approved
Pembrolizumab	PD-1	CPS ≥1 or MSI-H gastric/GEJ cancer (2nd line)	FDA-approved
Pembrolizumab + **Trastuzumab** + Chemo	HER2 + PD-1	HER2-positive unresectable/metastatic G/GEJ cancer (1st line)	FDA (accelerated)
Trastuzumab deruxtecan (DS-8201a)	HER2 (ADC)	HER2-positive G/GEJ cancer pretreated with trastuzumab	FDA-approved
Nivolumab	PD-1	Advanced/metastatic gastric/GEJ, 1st line with chemotherapy in PD-L1–positive tumors	FDA-approved
Zolbetuximab	CLDN18.2	CLDN18.2-positive/HER2-negative G/GEJ cancer	FDA approved

Table 12 Some of the most promising emerging targeted therapies in Gastric/GEJ Adenocarcinoma.

Therapy	Target	Indication	Phase
Zanidatamab (ZW25)	HER2 (bispecific)	HER2-positive gastric cancer	Phase II/III
Margetuximab	HER2 (Fc-optimized)	HER2-positive gastric cancer	Phase II
Bemarituzumab	FGFR2b	FGFR2b-positive gastric cancer	Phase III

Savolitinib, Telisotuzumab vedotin	MET	MET-amplified gastric cancer	Early Phase
RC48 (Disitamab vedotin)	HER2 (ADC)	HER2-low/positive G/GEJ (China-approved)	Not FDA-approved
Toripalimab + SOX/FOLFOX	PD-1	PD-L1+ advanced gastric cancer	Phase III
SHR-1701	PD-L1 + TGF-βRII	Gastric cancer (combination ICI)	Phase I/II
KN046	PD-L1 + CTLA-4	Gastric and other solid tumors	Phase II

5.2 Integration of Pathway Frequency Across Cancer Entities

Our thesis additionally laid some groundwork for cancer pathway identification and interaction. Pathway-level analysis was explored to better understand the molecular landscape of gastric adenocarcinoma in comparison to other cancer entities. Using the KEGG 'Pathways in Cancer' framework and publicly available data from The Cancer Genome Atlas (TCGA), a heatmap visualization in Table 7 was created to illustrate the frequency and distribution of targetable gene mutations across the most oncogenic signaling pathways in various cancer entities.

This table highlights that certain signaling pathways—such as PI3K/Akt, cell cycle regulation, RTK-RAS, and p53—are commonly dysregulated across a wide range of tumor types. But then there are other pathways which demonstrate more tumor-specific alteration patterns. Notably, these universally altered pathways control more fundamental processes such as proliferation, survival, apoptosis avoidance, and metabolic reprogramming, and therefore represent core mechanisms of tumor biology.

For gastric adenocarcinoma the most prominently altered pathways included Wnt/β-catenin, PI3K/Akt, RTK-RAS, p53, and TGF-β signaling. This finding associate with already existing literature and further emphasizes the multifactorial and heterogeneous nature of gastric tumorigenesis(Fattahi et al., 2020). In a variety of the other carcinomas a dominant oncogenic driver (e.g., BCR-ABL in CML or EGFR in NSCLC) can be identified, but gastric cancer tends to exhibit multiple pathway alterations rather than a single actionable mutation. This underlines the argument to pursue multi-pathway targeting approaches as well combination therapies in future research and clinical trials(Bass et al., 2014). An example would be those pathways such as estrogen receptor signaling or Hedgehog signaling are more selectively enriched in specific tumor types like breast, ovarian, or pancreatic cancer. In the meantime, DNA damage repair mechanisms, including base excision repair (BER) and PARP-mediated repair, show a

moderate but clinically significant distribution of targetable genes. These findings support the potential for exploiting synthetic lethality strategies in tumors with homologous recombination deficiency—including a subset of gastric cancers.

Then there are pathways such as MAPK, Notch, and JAK/STAT that have shown to be consistently altered across many cancer types. While their therapeutic utilization is known to be complex due to pathway redundancy and feedback mechanisms, these will remain important targets under active investigation(Degirmenci et al., 2020). Furthermore, signaling related to the tumor microenvironment—notably VEGF, HIF-1, and TGF-β—is also frequently dysregulated, reflecting the crucial role of angiogenesis, hypoxia adaptation, and immune modulation especially in high resistance carcinomas(Oya et al., 2020).

This pathway comparison across different cancer entities provides meaningful insight for drug development and clinical prioritization. In gastric cancer specifically, the prominence of mutations in pathways such as PI3K/Akt, Wnt/β-catenin, and RTK-RAS supports continued investigation into target. And as well as tumor microenvironment target the repeated involvement of p53 mutations and DNA repair deficiencies highlights opportunities for tumor suppressor reactivation strategies or the use of PARP inhibitors in selected patient populations.

The visualization also reinforces the importance to combine therapies, particularly where pathway crossways exist, such as combining PI3K or CDK inhibitors with immunotherapy in tumors exhibiting both oncogenic signaling and immune exclusion(Fattahi et al., 2020).

In summary, the pathway distribution patterns shown in Table 7 reflect both shared and specific molecular features of various cancer types. For gastric cancer, this reinforces the need for integrated, biomarker-driven approaches to treatment design. Enhancing our understanding of these pathways might accelerate the development of precision oncology strategies capable of addressing the complexity of GC.

5.3 Combination Network Analysis of Target Genes

In addition to pathway-level mapping, this thesis explored the relationship of molecular targets in gastric adenocarcinoma by analyzing co-targeting networks of the targeted therapies in clinical trials. The network diagram shown in Figure 13 illustrates the functional relationships and therapeutic combined targeting potential among genes. Nodes at the outer edge of the circle represent individual target genes identified in clinical trials, while edges indicate shared involvement in multiple therapeutic agents or signaling cascades. The varying edge stroke color intensity and thickness indicate the strength or frequency of co-targeting relationships.

Among the most prominent findings, ERBB2 (HER2) and PIK3CA emerged as central hub genes with the highest degree of connectivity, reflecting their crucial part in signaling cascades and their frequent inclusion in ongoing combination therapy trials for gastric cancer. Other

highly interconnected nodes and therefore often combined therapies included MET, FGFR2, AKT1, CDK4/6, and PDCD1 (PD-1). This emphasizes their influence across multiple cancer-relevant pathways. Immune checkpoint targets such as PDCD1 and CTLA4 were shown to cluster with intracellular signaling molecules like PI3K and Akt, supporting emerging clinical strategies that pair immunotherapy with targeted agents to enhance response rates with aim to reduce resistance.

In contrast, certain targets like CLDN18.2, SHC1, and SYK exhibited fewer interactions, suggesting these might be more tumor-specific alterations with potential for highly selective, biomarker-enriched treatment approaches. On the other hand, these targets are newly submerging therapies which have not yet been investigated in combination with other targets as they are in early phases.

Overall, this network-based analysis provides further evidence and illustration that gastric cancer is not driven by a single dominant oncogene, but rather by a complex web of interconnected molecular aberrations. As already stated, future treatment strategies may benefit from rationally designed combination regimens that target multiple co-altered pathways simultaneously, but this figure provides an overview of the most combined targets in clinical trials.

5.4 Limitations and challenges

While this thesis provides a comprehensive overview of targeted therapies in gastric adenocarcinoma, there are several limitations that must be acknowledged in the interpretation of its findings and implications.

Firstly, the scope of the analysis was limited to publicly accessible clinical trials only, most of which were registered on ClinicalTrials.gov and Adis Insight as well as supplemented by secondary literature databases. This may have excluded relevant international studies registered, which are more specific to certain regions such as the EU Clinical Trials Register or Chinese Clinical Trial Registry. As a result, some investigational therapies, particularly those in early development or non-English documentation, may have been excluded, potentially narrowing the breadth of the review.

Secondly, this work is based on a qualitative synthesis of available data rather than a quantitative meta-analysis. While it offers a broad mapping of gene targets, drug classes, and trial phases, it does not statistically compare outcomes across studies. As a result, this study does not attempt to rank therapies by efficacy or safety, nor does it evaluate progression-free survival or overall survival data across cohorts in a formal comparative manner. One reason for not evaluating and comparing results among trials was the heterogeneity in its biomarkers and reporting of the individual investigations. Trials evaluating PD-L1 expression, HER2 amplification, or CLDN18.2 positivity often use different thresholds and diagnostic assays,

complicating the interpretation and comparability of their results. The lack of standardization in biomarker measurement probably affects possibility to generalize and compare findings as well as applicate it straight into clinical practice

Moreover, the selection criteria for included studies may have introduced bias. Trials with limited protocol information, unavailable English translations, or restricted access were excluded, raising the possibility of selection and publication bias in the included data set.

Finally, this thesis reflects a time-limited snapshot of the rapidly evolving field of gastric oncology. Given the rate of discovery of new targets and options as well as trial progression, some these findings, specifically those in early phases, may soon or already are outdated or displaced by new data. Therefore, it will be necessary to continue monitoring and periodic reassessment to maintain clinical relevance.

Despite these limitations, this thesis offers a robust and structured analysis of the current landscape of targeted therapies for gastric adenocarcinoma and aims to serve as a valuable reference for future clinical and translational research.

5.5 Unexpected results of phase IV trials

Although all FDA approved therapies were excluded, there were still 64 phase IV trials found in this study. One possible reason, that there were still 64 trials in phase IV found, might be that the “phase” field in ClinicalTrials.gov is sponsor-reported and does not always map neatly onto U.S. FDA approval status for a specific indication. In addition, the data collection and curation of the drug list and trial dataset occurred over an extended period (November 1, 2020, to January 30th, 2022), during which approvals, protocol amendments, and registry updates may have changed how trials were labelled or indexed, so a subset of records may reflect evolving regulatory status or reclassified trial phases or even some of the therapies might have gotten approved by FDA in the meantime. Further explanations include that phase IV labels are reflecting post-marketing studies outside the U.S. (i.e., post-approval under EMA/PMDA/NMPA rather than FDA), pragmatic safety/effectiveness studies or registries that are occasionally tagged as Phase IV even when the intervention is being used off-label or in a new combination and was not approved prior, and imperfect mapping of agent names (brand/generic/code names) when trials list a combination regimen.

5.6 Outlook into the future

After looking at limitations and challenges, future trials should attempt to incorporate more adaptive designs, publicly available basket and umbrella protocols, and a higher emphasis on biomarker-enriched stratification to better capture the biological complexity and heterogeneity of gastric cancer. These innovations combined with next-generation diagnostics and computational tools, will enable more efficient and individualized treatment strategies in the

future. The following avenues are likely to shape the future landscape of research and clinical practice for gastric cancer over the next few years.

5.6.1 Basket and platform trials

In response to this complexity, future trials are increasingly adopting master-protocol designs (basket, umbrella, and platform trials) that pair broad molecular screening with multiple biomarker-defined treatment arms. The NCI-MATCH trial (NCT02465060) demonstrated the feasibility of centrally screening large numbers of patients across tumor types and assigning them to molecularly matched sub studies, while also highlighting real-world bottlenecks such as limited tissue, turnaround times, low prevalence of individual alterations, and attrition between profiling and treatment initiation(Flaherty et al., 2020). Building on these lessons, the successor platform ComboMATCH (NCT05564377) (National Cancer Institute, 2026) explicitly evaluates rational drug combinations to address resistance mechanisms and includes both tumor-agnostic and tumor-specific cohorts. For gastric adenocarcinoma, integrating such basket-style infrastructures with harmonized biomarker assays (e.g., IHC/FISH/NGS) could reduce failed screening and accelerate evaluation of emerging targets such as CLDN18.2, FGFR2b, MET, and DNA-repair alterations.

Collectively, these platform trials illustrate that the main limitation is not the availability of targeted agents, but the feasibility and yield of large-scale biomarker screening including tissue adequacy, assay harmonization, and rarity of alterations, which directly determines enrollment into biomarker-enriched arms.

5.6.2 Novel Biomarkers and Molecular Subtyping

While HER2, PD-L1, MSI/dMMR, and CLDN18.2 are currently the most clinically actionable biomarkers, future research will need to expand beyond this panel and, importantly, standardize how biomarkers are measured and reported. In practical terms, an updated baseline work-up in advanced disease increasingly requires coordinated testing by immunohistochemistry (HER2, PD-L1 CPS, CLDN18.2, FGFR2b), in situ hybridization when indicated (HER2 amplification, MET amplification), and next-generation sequencing to capture actionable alterations and emerging resistance mechanisms(Lordick et al., 2022).

Tumor mutational burden (TMB) and homologous recombination deficiency (HRD) represent additional layers of biology that may guide trial enrollment in selected patients (e.g., tissue-agnostic immunotherapy for TMB-high tumors or PARP inhibitor strategies for HRD)(Marcus et al., 2021). Epigenetic alterations and transcriptomic signatures are also being explored to better define immune phenotypes ("hot" vs "cold" tumors) and stromal subtypes, which may inform combination strategies such as PD-1 blockade with VEGF/FGF axis inhibition or TGF-β pathway modulation. Integrative multi-omics profiling (genomic, transcriptomic, proteomic,

and epigenetic data) is therefore likely to refine molecular subtyping beyond TCGA/ACRG and help rationalize treatment sequencing(J.-S. Lee, 2026).

Epigenetic alterations, including promoter methylation and histone modification, are increasingly recognized as drivers of gastric tumorigenesis, but hard to target without resistance and accommodating safety. But overall these may serve not only as biomarkers but also as direct therapeutic targets(Demicco et al., 2011). To fully explore these options, integrative multi-omics profiling like combining genomic, transcriptomic, proteomic, and epigenetic data, will be essential. This will help refine molecular subtypes of gastric cancer and guide personalized treatment beyond current classifications like TCGA.

5.6.3 Antibody-Drug Conjugates (ADCs)

ADCs represent one of the most promising classes of emerging cancer therapies with no need for developing new targets as they are delivering cytotoxic agents directly to tumor cells via antibody targeting. The clinical success of trastuzumab deruxtecan (T-DXd) in HER2-positive gastric cancer has revived interest into this alternative. Additional ADCs, such as RC48 (disitamab vedotin), are currently in late-phase development and have demonstrated encouraging results in both HER2-low and HER2-positive tumors(Y. Xu et al., 2021).
Future ADCs are in development to target CLDN18.2, MET, and FGFR2. Each of these targets is enriched in specific molecular subsets of gastric adenocarcinoma. Early clinical signals from first-in-human studies suggest that optimizing antigen density thresholds, linker stability, and payload selection will be critical to maximize efficacy while limiting systemic toxicity (Katoh et al., 2025). These agents may be particularly valuable in refractory disease or after resistance to antibody or checkpoint-based regimens.

5.6.4 Tumor Microenvironment Modulation

The tumor microenvironment (TME) in gastric cancer is particularly complex, characterized by fibrosis, hypoxia, and a suppressive immune milieu. Key components include regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), and tumor-associated macrophages (TAMs), which all inhibit effective antitumor immunity(Yasuda & Wang, 2024).
But therapeutic designs aimed at reprogramming the TME are gaining traction to overcome resistance. For example, CSF1R inhibitors may deplete immunosuppressive macrophages, while CXCR4 antagonists could facilitate the infiltration of cytotoxic T cells into the tumor. Combining such agents with checkpoint inhibitors may restore immune responsiveness, especially in tumors which have been previously unresponsive to immunotherapy(Ding et al., 2020).

Further exploration into other choices like angiogenesis inhibitors, stromal remodeling agents, and metabolic modulators (e.g., IDO1 inhibitors) could also shift the immunologic balance of the TME and enhance overall therapeutic outcomes.

5.6.5 Personalized Immunotherapy

Personalized immunotherapy, including CAR-T cell therapy and neoantigen-based vaccines, offers a new frontier for gastric cancer treatment, though the conversion into solid tumors remains challenging not only in gastric cancer(Marofi et al., 2021). In contrast to hematologic malignancies, solid tumors such as gastric cancer are confronted by barriers like antigen heterogeneity, TME-induced T cell exhaustion, and physical barriers to T cell infiltration(T. Yan, Zhu, & Chen, 2023).

Nonetheless, early-phase trials investigating CAR-T cells aimed at CLDN18.2, HER2, and CEA are underway(Barrett et al., 2024; Qi et al., 2024). Additionally, local or regional delivery strategies and combination regimens may help overcome some of these barriers.

Personalized cancer vaccines were left out of this study but are designed based on patient-specific neoantigens identified via whole-exome sequencing and are also in preclinical and early clinical development(Q. Liu et al., 2022). These vaccines might be particularly effective when used alongside checkpoint inhibitors or adoptive T cell therapies, offering a lasting immune memory and long-term disease control. In gastric cancer, these approaches may be most relevant in molecular subsets with higher neoantigen burden (e.g., MSI-H) or in settings where minimal residual disease can be monitored and targeted longitudinally using ctDNA(X. Li et al., 2023).

5.6.6 Artificial Intelligence and Predictive Modeling

As the complexity of gastric cancer biology increases, so does the need for advanced analytical tools. Artificial intelligence (AI) and machine learning (ML) are composed to revolutionize how clinical, genomic, and imaging data is assessed(Qin, Deng, Jiang, Hu, & Song, 2021). By integrating datasets across radiomics, digital pathology, genomics, and electronic health records, AI might be able to help with predicting treatment response in selected patients, identifying new biomarkers, evaluating patients for clinical trials, and optimizing treatment sequencing.

For example, radiomic features extracted from CT or PET scans may correlate with molecular subtypes or TME composition(Zhi et al., 2024). Correspondingly, machine learned based image analysis of pathology slides can assist in identifying subtle biomarker patterns that might escape human interpretation and be more standardized(Y. Deng et al., 2022).

These technologies might be able support real-time decision-making in both clinical trials and practice in the future, enabling adjusted treatment plans tailored to evolving tumor characteristics especially in such a heterogenic entity as gastric carcinoma(R. Li et al., 2025).

5.6.7 Summary

In conclusion, this thesis maps the evolving landscape of targeted therapy development in gastric adenocarcinoma and highlights actionable trends in trial design, molecular targeting, and future therapeutic strategies. Overall, 2433 clinical trials were identified, comprising 905 investigational therapeutic agents directed against 320 distinct gene or protein targets, thereby providing a structured reference for research prioritization and the rational design of future biomarker-driven studies.

The future of gastric cancer treatment lies in integrated, biomarker-informed therapies and trial concepts that efficiently match patients to molecularly defined treatment strategies. This thesis affirms that while HER2 and PD-L1 remain key biomarkers in clinical decision-making, CLDN18.2 has now entered first-line practice in the United States following the FDA approval of zolbetuximab-clzb with fluoropyrimidine- and platinum-based chemotherapy for CLDN18.2-positive, HER2-negative advanced gastric/GEJ adenocarcinoma. Targets such as FGFR2b and MET remain among the most advanced candidates to further expand precision strategies, pending confirmatory data and regulatory evaluation. At the same time, antibody–drug conjugates continue to represent one of the most promising modalities for extending targeted approaches, particularly in resistance settings.

Furthermore, the thesis underscores that patient selection remains a central bottleneck, as biomarker testing is limited by heterogeneity, assay variability, and feasibility of large-scale screening in routine care. In this context, master-protocol “basket” strategies provide a practical framework to accelerate development and improve evidence generation in rare molecular subsets, as exemplified by NCI-MATCH (NCT02465060) and the ongoing successor platform ComboMATCH (NCT05564377), which aims to evaluate rational combination strategies to address resistance mechanisms. Further work is needed to validate these findings in broader and more diverse populations, to standardize biomarker assays and eligibility thresholds, and to ensure that advances in targeted therapies translate into clinically meaningful, globally accessible, and sustainable treatment options for patients with gastric adenocarcinoma.

6 References

AACR, W. C. R. F. A. I. f. C. R. (2018). *Continuous Update Project Expert Report 2018. Diet, nutrition, physical activity and stomach cancer.* Retrieved from dietandcancerreport.org

Abdi, E., Latifi-Navid, S., Zahri, S., Yazdanbod, A., & Pourfarzi, F. (2019). Risk factors predisposing to cardia gastric adenocarcinoma: Insights and new perspectives. *Cancer Medicine, 8*(13), 6114-6126. doi:https://doi.org/10.1002/cam4.2497

Abnet, C. C., Freedman, N. D., Hu, N., Wang, Z., Yu, K., Shu, X.-O., . . . Taylor, P. R. (2010). A shared susceptibility locus in PLCE1 at 10q23 for gastric adenocarcinoma and esophageal squamous cell carcinoma. *Nature Genetics, 42*(9), 764-767. doi:10.1038/ng.649

Abrahao-Machado, L. F., & Scapulatempo-Neto, C. (2016). HER2 testing in gastric cancer: An update. *World journal of gastroenterology, 22*(19), 4619-4625. doi:10.3748/wjg.v22.i19.4619

Abrams, J. A., Gonsalves, L., & Neugut, A. I. (2013). Diverging Trends in the Incidence of Reflux-related and Helicobacter pylori-related Gastric Cardia Cancer. *Journal of Clinical Gastroenterology, 47*(4), 322-327. doi:10.1097/MCG.0b013e318260177a

Adenis, A., Blay, J. Y., Bui-Nguyen, B., Bouché, O., Bertucci, F., Isambert, N., . . . Le Cesne, A. (2014). Masitinib in advanced gastrointestinal stromal tumor (GIST) after failure of imatinib: a randomized controlled open-label trial. *Ann Oncol, 25*(9), 1762-1769. doi:10.1093/annonc/mdu237

Agrawal, N., Akbani, R., Aksoy, B. A., Ally, A., Arachchi, H., Asa, S. L., . . . Zou, L. (2014). Integrated Genomic Characterization of Papillary Thyroid Carcinoma. *Cell, 159*(3), 676-690. doi:10.1016/j.cell.2014.09.050

Ahmed, N. (2005). 23 years of the discovery of Helicobacter pylori: Is the debate over? *Annals of Clinical Microbiology and Antimicrobials, 4*(1), 17. doi:10.1186/1476-0711-4-17

Ajani, J. A., D'Amico, T. A., Almhanna, K., Bentrem, D. J., Chao, J., Das, P., . . . Sundar, H. (2016). Gastric Cancer, Version 3.2016, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw, 14*(10), 1286-1312. doi:10.6004/jnccn.2016.0137

Al-Batran, S.-E., Homann, N., Pauligk, C., Goetze, T. O., Meiler, J., Kasper, S., . . . Luley, K. (2019). 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. *The Lancet, 393*(10184), 1948-1957. doi:10.1016/s0140-6736(18)32557-1

Al-Batran, S. E., Pauligk, C., Homann, N., Hartmann, J. T., Moehler, M., Probst, S., . . . Jäger, E. (2013). The feasibility of triple-drug chemotherapy combination in older adult patients with oesophagogastric cancer: a randomised trial of the Arbeitsgemeinschaft Internistische Onkologie (FLOT65+). *Eur J Cancer, 49*(4), 835-842. doi:10.1016/j.ejca.2012.09.025

Albadari, N., Deng, S., & Li, W. (2019). The transcriptional factors HIF-1 and HIF-2 and their novel inhibitors in cancer therapy. *Expert Opin Drug Discov, 14*(7), 667-682. doi:10.1080/17460441.2019.1613370

Amin, M. B., Greene, F. L., Edge, S. B., Compton, C. C., Gershenwald, J. E., Brookland, R. K., . . . Winchester, D. P. (2017). The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. *CA: A Cancer Journal for Clinicians, 67*(2), 93-99. doi:https://doi.org/10.3322/caac.21388

An, J. Y., Kang, T. H., Choi, M. G., Noh, J. H., Sohn, T. S., & Kim, S. (2008). Borrmann type IV: an independent prognostic factor for survival in gastric cancer. *J Gastrointest Surg, 12*(8), 1364-1369. doi:10.1007/s11605-008-0516-9

Anderson, W. F., Rabkin, C. S., Turner, N., Fraumeni, J. F., Jr, Rosenberg, P. S., & Camargo, M. C. (2018). The Changing Face of Noncardia Gastric Cancer Incidence Among US Non-Hispanic Whites. *JNCI: Journal of the National Cancer Institute, 110*(6), 608-615. doi:10.1093/jnci/djx262

Apicella, M., Corso, S., Giordano, S., Apicella, M., Corso, S., & Giordano, S. (2017). Targeted therapies for gastric cancer: failures and hopes from clinical trials. *Oncotarget, 8*(34), 57654-57669. doi:10.18632/ONCOTARGET.14825

Bagegni, N. A., Park, H., Kraft, K., M, O. T., Gao, F., Waqar, S. N., . . . Wang-Gillam, A. (2022). Phase 1b trial of anti-VEGF/PDGFR vorolanib combined with immune checkpoint inhibitors in patients with advanced solid tumors. *Cancer Chemother Pharmacol, 89*(4), 487-497. doi:10.1007/s00280-022-04406-6

Bahleda, R., Meric-Bernstam, F., Goyal, L., Tran, B., He, Y., Yamamiya, I., . . . Arkenau, H. T. (2020). Phase I, first-in-human study of futibatinib, a highly selective, irreversible FGFR1-4 inhibitor in patients with advanced solid tumors. *Ann Oncol, 31*(10), 1405-1412. doi:10.1016/j.annonc.2020.06.018

Balakrishnan, M., George, R., Sharma, A., & Graham, D. Y. (2017). Changing Trends in Stomach Cancer Throughout the World. *Current Gastroenterology Reports, 19*(8), 36. doi:10.1007/s11894-017-0575-8

Bang, Y. J., Kang, Y. K., Catenacci, D. V., Muro, K., Fuchs, C. S., Geva, R., . . . Chung, H. C. (2019). Pembrolizumab alone or in combination with chemotherapy as first-line therapy for patients with advanced gastric or gastroesophageal junction adenocarcinoma: results from the phase II nonrandomized KEYNOTE-059 study. *Gastric Cancer, 22*(4), 828-837. doi:10.1007/S10120-018-00909-5/FIGURES/2

Bang, Y. J., Van Cutsem, E., Feyereislova, A., Chung, H. C., Shen, L., Sawaki, A., . . . Kang, Y. K. (2010). 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. *The Lancet, 376*(9742), 687-697. doi:10.1016/S0140-6736(10)61121-X

Barrett, A. M., Britton, Z. T., Carrasco, R. A., Breen, S., Broggi, M. A. S., Hatke, A. L., . . . Bosco, E. E. (2024). Preclinical Evaluation of AZD6422, an Armored Chimeric Antigen Receptor T Cell Targeting CLDN18.2 in Gastric, Pancreatic, and Esophageal Cancers. *Clinical Cancer Research, 30*(23), 5413-5429. doi:10.1158/1078-0432.Ccr-24-1853

Bartley, A. N., Washington, M. K., Colasacco, C., Ventura, C. B., Ismaila, N., Benson, A. B., 3rd, . . . Ajani, J. A. (2017). HER2 Testing and Clinical Decision Making in Gastroesophageal Adenocarcinoma: Guideline From the College of American Pathologists, American Society for Clinical Pathology, and the American Society of Clinical Oncology. *J Clin Oncol, 35*(4), 446-464. doi:10.1200/jco.2016.69.4836

Bartley, A. N., Washington, M. K., Colasacco, C., Ventura, C. B., Ismaila, N., Benson, A. B., . . . Ajani, J. A. (2016). HER2 Testing and Clinical Decision Making in Gastroesophageal Adenocarcinoma: Guideline From the College of American Pathologists, American Society for Clinical Pathology, and the American Society of Clinical Oncology. *Journal of Clinical Oncology, 35*(4), 446-464. doi:10.1200/JCO.2016.69.4836

Bass, A. J., Thorsson, V., Shmulevich, I., Reynolds, S. M., Miller, M., Bernard, B., . . . Center, U. N. C. L. C. C. (2014). Comprehensive molecular characterization of gastric adenocarcinoma. *Nature, 513*(7517), 202-209. doi:10.1038/nature13480

Bauer, T., Cho, B. C., Heist, R., Bazhenova, L., Werner, T., Goel, S., . . . Pant, S. (2022). First-in-human phase 1/1b study to evaluate sitravatinib in patients with advanced solid tumors. *Invest New Drugs*. doi:10.1007/s10637-022-01274-y

Bertuccio, P., Alicandro, G., Rota, M., Pelucchi, C., Bonzi, R., Galeone, C., . . . La Vecchia, C. (2019). Citrus fruit intake and gastric cancer: The stomach cancer pooling (StoP) project consortium. *International Journal of Cancer, 144*(12), 2936-2944. doi:https://doi.org/10.1002/ijc.32046

Boland, C. R., & Yurgelun, M. B. (2017). Historical Perspective on Familial Gastric Cancer. *Cellular and Molecular Gastroenterology and Hepatology, 3*(2), 192-200. doi:https://doi.org/10.1016/j.jcmgh.2016.12.003

Borrmann, R. (1926). Makroskopische Formen des vortgeschritteten Magenkrebses. In F. Henke & O. Lubarsch (Eds.), *Handbuch der speziellen Anatomie und Histologie* (Vol. 4). Berlin: Springer.

Borthakur, G., Ofran, Y., Tallman, M. S., Foran, J., Uy, G. L., DiPersio, J. F., . . . Andreeff, M. (2021). BL-8040 CXCR4 antagonist is safe and demonstrates antileukemic activity in combination with cytarabine for the treatment of relapsed/refractory acute myelogenous leukemia: An open-label safety and efficacy phase 2a study. *Cancer, 127*(8), 1246-1259. doi:https://doi.org/10.1002/cncr.33338

Bosman, F. T., Carneiro, F., Hruban, R. H., & Theise, N. D. (2010). *WHO classification of tumours of the digestive system*: World Health Organization.

Boussios, S., Karihtala, P., Moschetta, M., Abson, C., Karathanasi, A., Zakynthinakis-Kyriakou, N., . . . Pavlidis, N. (2020). Veliparib in ovarian cancer: a new synthetically lethal therapeutic approach. *Invest New Drugs, 38*(1), 181-193. doi:10.1007/s10637-019-00867-4

Boysen, T., Mohammadi, M., Melbye, M., Hamilton-Dutoit, S., Vainer, B., Hansen, A. V., . . . Friborg, J. (2009). EBV-associated gastric carcinoma in high- and low-incidence areas for nasopharyngeal carcinoma. *British Journal of Cancer, 101*(3), 530-533. doi:10.1038/sj.bjc.6605168

Brown, J. S., O'Carrigan, B., Jackson, S. P., & Yap, T. A. (2017). Targeting DNA Repair in Cancer: Beyond PARP Inhibitors. *Cancer Discovery, 7*(1), 20-37. doi:10.1158/2159-8290.CD-16-0860

Burgess, D. E., Woodman, C. B., Flavell, K. J., Rowlands, D. C., Crocker, J., Scott, K., . . . Murray, P. G. (2002). Low prevalence of Epstein–Barr virus in incident gastric adenocarcinomas from the United Kingdom. *British Journal of Cancer, 86*(5), 702-704. doi:10.1038/sj.bjc.6600107

Camargo, M. C., Anderson, W. F., King, J. B., Correa, P., Thomas, C. C., Rosenberg, P. S., . . . Rabkin, C. S. (2011). Divergent trends for gastric cancer incidence by anatomical subsite in US adults. *Gut, 60*(12), 1644-1649. doi:10.1136/gut.2010.236737

Cao, B., Wang, Q., Fu, X. L., Wei, G. D., Zhao, L., Zhang, P. J., . . . Zhang, Q. (2021). The efficacy and safety of neoadjuvant nimotuzumab for gastric cancer: A meta-analysis of randomized controlled studies. *Medicine (Baltimore), 100*(50), e27709. doi:10.1097/md.0000000000027709

Carmeliet, P. (2005). VEGF as a key mediator of angiogenesis in cancer. *Oncology, 69 Suppl 3*, 4-10. doi:10.1159/000088478

Catenacci, D. V., Rosales, M., Chung, H. C., H, H. Y., Shen, L., Moehler, M., & Kang, Y. K. (2021). MAHOGANY: margetuximab combination in HER2+ unresectable/metastatic gastric/gastroesophageal junction adenocarcinoma. *Future Oncol, 17*(10), 1155-1164. doi:10.2217/fon-2020-1007

Catenacci, D. V. T., Rasco, D., Lee, J., Rha, S. Y., Lee, K. W., Bang, Y. J., . . . Wainberg, Z. A. (2020). Phase I Escalation and Expansion Study of Bemarituzumab (FPA144) in Patients With Advanced Solid Tumors and FGFR2b-Selected Gastroesophageal Adenocarcinoma. *J Clin Oncol, 38*(21), 2418-2426. doi:10.1200/jco.19.01834

Cats, A., Jansen, E. P. M., van Grieken, N. C. T., Sikorska, K., Lind, P., Nordsmark, M., . . . Verheij, M. (2018). Chemotherapy versus chemoradiotherapy after surgery and preoperative chemotherapy for resectable gastric cancer (CRITICS): an international, open-label, randomised phase 3 trial. *Lancet Oncol, 19*(5), 616-628. doi:10.1016/s1470-2045(18)30132-3

Cattelan, L., Ghazawi, F. M., Le, M., Lagacé, F., Rahme, E., Zubarev, A., . . . Netchiporouk, E. (2021). Geographic and Socioeconomic Disparity of Gastric Cancer Patients in Canada. *Current Oncology, 28*(3), 2052-2064. Retrieved from https://www.mdpi.com/1718-7729/28/3/190

Cerami, E. G., Gross, B. E., Demir, E., Rodchenkov, I., Babur, O., Anwar, N., . . . Sander, C. (2011). Pathway Commons, a web resource for biological pathway data. *Nucleic Acids Res, 39*(Database issue), D685-690. doi:10.1093/nar/gkq1039

Chang, C.-J., Tu, Y.-K., Chen, P.-C., & Yang, H.-Y. (2020). Talc exposure and risk of stomach cancer: Systematic review and meta-analysis of occupational cohort studies. *Journal of the Formosan Medical Association, 119*(4), 781-792. doi:https://doi.org/10.1016/j.jfma.2018.07.015

Chen, Y. L., Law, P. Y., & Loh, H. H. (2005). Inhibition of PI3K/Akt signaling: an emerging paradigm for targeted cancer therapy. *Curr Med Chem Anticancer Agents, 5*(6), 575-589. doi:10.2174/156801105774574649

Cheng, X. J., Lin, J. C., & Tu, S. P. (2016). Etiology and Prevention of Gastric Cancer. *Gastrointestinal Tumors, 3*(1), 25-36. doi:10.1159/000443995

Chon, H. J., Hyung, W. J., Kim, C., Park, S., Kim, J.-H., Park, C. H., . . . Jeung, H.-C. (2017). Differential Prognostic Implications of Gastric Signet Ring Cell Carcinoma: Stage Adjusted Analysis From a Single High-volume Center in Asia. *Annals of Surgery, 265*(5), 946-953. doi:10.1097/sla.0000000000001793

Choudhury, A. D., Higano, C. S., de Bono, J. S., Cook, N., Rathkopf, D. E., Wisinski, K. B., . . . Hansen, A. R. (2022). A Phase I Study Investigating AZD8186, a Potent and Selective Inhibitor of PI3Kβ/δ, in Patients with Advanced Solid Tumors. *Clin Cancer Res, 28*(11), 2257-2269. doi:10.1158/1078-0432.Ccr-21-3087

Chung, V., Wang, L., Fletcher, M. S., Massarelli, E., Cristea, M. C., Kamaraju, S., . . . Wu, J. (2021). First-time in-human study of VMD-928, an oral allosteric TrkA selective inhibitor targeting TrkA protein overexpression, in patients with solid tumors or lymphoma. *Journal of Clinical Oncology, 39*(15_suppl), 3081-3081. doi:10.1200/JCO.2021.39.15_suppl.3081

Clark, C. J., Thirlby, R. C., Picozzi, V., Schembre, D. B., Cummings, F. P., & Lin, E. (2006). Current Problems in Surgery: Gastric Cancer. *Current Problems in Surgery, 43*(8), 566-670. doi:https://doi.org/10.1067/j.cpsurg.2006.06.003

Cleary, J. M., Aguirre, A. J., Shapiro, G. I., & D'Andrea, A. D. (2020). Biomarker-Guided Development of DNA Repair Inhibitors. *Molecular cell, 78*(6), 1070-1085. doi:10.1016/j.molcel.2020.04.035

clinicaltrials.gov. (2022). Resources and Trends. Retrieved from https://clinicaltrials.gov/ct2/resources/trends

Cluzeau, T., Sebert, M., Rahmé, R., Cuzzubbo, S., Lehmann-Che, J., Madelaine, I., . . . Fenaux, P. (2021). Eprenetapopt Plus Azacitidine in TP53-Mutated Myelodysplastic Syndromes and Acute Myeloid Leukemia: A Phase II Study by the Groupe Francophone des Myélodysplasies (GFM). *J Clin Oncol, 39*(14), 1575-1583. doi:10.1200/jco.20.02342

Colak, S., & Ten Dijke, P. (2017). Targeting TGF-β Signaling in Cancer. *Trends Cancer, 3*(1), 56-71. doi:10.1016/j.trecan.2016.11.008

Collins, G. P., Clevenger, T. N., Burke, K. A., Yang, B., MacDonald, A., Cunningham, D., . . . Flinn, I. (2021). A phase 1/2 study of the combination of acalabrutinib and vistusertib in patients with relapsed/refractory B-cell malignancies. *Leuk Lymphoma, 62*(11), 2625-2636. doi:10.1080/10428194.2021.1938027

Crawford, K., Bontrager, E., Schwarz, M. A., Chaturvedi, A., Lee, D. D., Md Sazzad, H., . . . Awasthi, N. (2021). Targeted FGFR/VEGFR/PDGFR inhibition with dovitinib enhances the effects of nab-paclitaxel in preclinical gastric cancer models. *Cancer Biol Ther, 22*(10-12), 619-629. doi:10.1080/15384047.2021.2011642

Cristescu, R., Lee, J., Nebozhyn, M., Kim, K.-M., Ting, J. C., Wong, S. S., . . . Aggarwal, A. (2015). Molecular analysis of gastric cancer identifies subtypes associated with distinct clinical outcomes. *Nature Medicine, 21*(5), 449-456. doi:10.1038/nm.3850

Cunningham, D., Allum, W. H., Stenning, S. P., Thompson, J. N., Van de Velde, C. J. H., Nicolson, M., . . . Chua, Y. J. (2006). Perioperative Chemotherapy versus Surgery Alone for Resectable Gastroesophageal Cancer. *New England Journal of Medicine, 355*(1), 11-20. doi:10.1056/NEJMoa055531

Cunningham, D., Starling, N., Rao, S., Iveson, T., Nicolson, M., Coxon, F., . . . Norman, A. R. (2008). Capecitabine and oxaliplatin for advanced esophagogastric cancer. *N Engl J Med, 358*(1), 36-46. doi:10.1056/NEJMoa073149

D'Huyvetter, M., Vos, J., Caveliers, V., Vaneycken, I., Heemskerk, J., Duhoux, F. P., . . . Keyaerts, M. (2021). Phase I Trial of (131)I-GMIB-Anti-HER2-VHH1, a New Promising Candidate for HER2-Targeted Radionuclide Therapy in Breast Cancer Patients. *J Nucl Med, 62*(8), 1097-1105. doi:10.2967/jnumed.120.255679

Dal-Ré, R., Banzi, R., Cristea, I. A., Fernández-de-las-Peñas, C., Hemkens, L. G., Janiaud, P., . . . Rosendaal, F. R. (2023). Using the phases of clinical development of medicines to describe clinical trials assessing other interventions is widespread but not useful. *Journal of Clinical Epidemiology, 161*, 157-163. doi:https://doi.org/10.1016/j.jclinepi.2023.07.011

Dawson, J. C., Serrels, A., Stupack, D. G., Schlaepfer, D. D., & Frame, M. C. (2021). Targeting FAK in anticancer combination therapies. *Nature reviews. Cancer, 21*(5), 313-324. doi:10.1038/s41568-021-00340-6

De Mello, R. A., Lordick, F., Muro, K., & Janjigian, Y. Y. (2019). Current and Future Aspects of Immunotherapy for Esophageal and Gastric Malignancies. *Am Soc Clin Oncol Educ Book, 39*, 237-247. doi:10.1200/edbk_236699

de Vries Schultink, A. H. M., Bol, K., Doornbos, R. P., Murat, A., Wasserman, E., Dorlo, T. P. C., . . . Huitema, A. D. R. (2020). Population Pharmacokinetics of MCLA-128, a HER2/HER3 Bispecific Monoclonal Antibody, in Patients with Solid Tumors. *Clin Pharmacokinet, 59*(7), 875-884. doi:10.1007/s40262-020-00858-2

Degirmenci, U., Wang, M., & Hu, J. (2020). Targeting Aberrant RAS/RAF/MEK/ERK Signaling for Cancer Therapy. *Cells, 9*(1), 198. doi:10.3390/cells9010198

Demicco, E. G., Farris, A. B., Baba, Y., Agbor-Etang, B., Bergethon, K., Mandal, R., . . . Mino-Kenudson, M. (2011). The dichotomy in carcinogenesis of the distal esophagus and esophagogastric junction: intestinal-type vs cardiac-type mucosa-associated adenocarcinoma. *Modern Pathology, 24*(9), 1177-1190. doi:10.1038/modpathol.2011.77

Deng, J., Chernikova, S. B., Wang, Y., Rodriguez, M. L., Andersen, S. J., Umeh-Garcia, M. C., . . . Gephart, M. H. (2021). A Novel Brain-Permeant Chemotherapeutic Agent for the Treatment of Brain Metastasis in Triple-Negative Breast Cancer. *Mol Cancer Ther, 20*(11), 2110-2116. doi:10.1158/1535-7163.Mct-21-0140

Deng, Y., Qin, H. Y., Zhou, Y. Y., Liu, H. H., Jiang, Y., Liu, J. P., & Bao, J. (2022). Artificial intelligence applications in pathological diagnosis of gastric cancer. *Heliyon, 8*(12), e12431. doi:10.1016/j.heliyon.2022.e12431

Denoix, P. (1952). Nomenclature classification des cancers. *Bull. Inst. Nat. Hyg.(Paris), 7*, 743-748.

Derakhshan, M. H., Malekzadeh, R., Watabe, H., Yazdanbod, A., Fyfe, V., Kazemi, A., . . . McColl, K. E. L. (2008). Combination of gastric atrophy, reflux symptoms and histological subtype indicates two distinct aetiologies of gastric cardia cancer. *Gut, 57*(3), 298-305. doi:10.1136/gut.2007.137364

Dias, M. P., Moser, S. C., Ganesan, S., & Jonkers, J. (2021). Understanding and overcoming resistance to PARP inhibitors in cancer therapy. *Nat Rev Clin Oncol, 18*(12), 773-791. doi:10.1038/s41571-021-00532-x

Ding, J., Yao, Y., Huang, G., Wang, X., Yi, J., Zhang, N., . . . Cheng, H. (2020). Targeting the EphB4 receptor tyrosine kinase sensitizes HER2-positive breast cancer cells to Lapatinib. *Cancer Letters, 475*, 53-64. doi:https://doi.org/10.1016/j.canlet.2020.01.032

Djureinovic, D., Wang, M., & Kluger, H. M. (2021). Agonistic CD40 Antibodies in Cancer Treatment. *Cancers (Basel), 13*(6). doi:10.3390/cancers13061302

Dos Santos, M., Lequesne, J., Leconte, A., Corbinais, S., Parzy, A., Guilloit, J. M., . . . Clarisse, B. (2022). Perioperative treatment in resectable gastric cancer with spartalizumab in combination with fluorouracil, leucovorin, oxaliplatin and docetaxel (FLOT): a phase II study (GASPAR). *BMC Cancer, 22*(1), 537. doi:10.1186/s12885-022-09623-z

Drugbank Online. (2022). About Drugbank online. Retrieved from https://go.drugbank.com/about

Duffy, M. J., Synnott, N. C., & Crown, J. (2017). Mutant p53 as a target for cancer treatment. *Eur J Cancer, 83*, 258-265. doi:10.1016/j.ejca.2017.06.023

Dykewicz, C. A. (2001). Summary of the Guidelines for Preventing Opportunistic Infections among Hematopoietic Stem Cell Transplant Recipients. *Clin Infect Dis, 33*(2), 139-144. doi:10.1086/321805

Easaw, J. C., Lim, H. J., Karachiwala, H., Gill, S., Zhu, X., & Bateman, J. (2025). Zolbetuximab or Immunotherapy as the Initial Targeted Therapy in CLDN18.2-Positive, HER2-Negative Advanced Gastric Cancer: Weighing the Options. *Curr Oncol, 32*(11). doi:10.3390/curroncol32110648

Everett, S. M., & Axon, A. T. R. (1997). Early gastric cancer in Europe. *Gut, 41*(2), 142-150. doi:10.1136/gut.41.2.142

Evrard, C., Louvet, C., Hajbi, F. E., Fiore, F. D., Malicot, K. L., Aparicio, T., . . . Tougeron, D. (2021). PRODIGE 59-DURIGAST trial: A randomised phase II study evaluating FOLFIRI + Durvalumab ± Tremelimumab in second-line of patients with advanced gastric cancer. *Dig Liver Dis, 53*(4), 420-426. doi:10.1016/j.dld.2020.11.036

Eyre, T. A., Hildyard, C., Hamblin, A., Ali, A. S., Houlton, A., Hopkins, L., . . . Collins, G. P. (2019). A phase II study to assess the safety and efficacy of the dual mTORC1/2 inhibitor vistusertib in relapsed, refractory DLBCL. *Hematol Oncol, 37*(4), 352-359. doi:10.1002/hon.2662

Falchook, G. S., Bendell, J. C., Ulahannan, S. V., Sen, S., Vilimas, R., Kriksciukaite, K., . . . Thomas, A. (2020). Pen-866, a miniature drug conjugate of a heat shock protein 90 (HSP90) ligand linked to SN38 for patients with advanced solid malignancies: Phase I and expansion cohort results. *Journal of Clinical Oncology, 38*(15_suppl), 3515-3515. doi:10.1200/JCO.2020.38.15_suppl.3515

Falzone, L., Salomone, S., & Libra, M. (2018). Evolution of Cancer Pharmacological Treatments at the Turn of the Third Millennium. *Frontiers in Pharmacology, 9*(1300). doi:10.3389/fphar.2018.01300

Fang, D. D., Tang, Q., Kong, Y., Rong, T., Wang, Q., Li, N., . . . Zhai, Y. (2021). MDM2 inhibitor APG-115 exerts potent antitumor activity and synergizes with standard-of-care agents in preclinical acute myeloid leukemia models. *Cell Death Discov, 7*(1), 90. doi:10.1038/s41420-021-00465-5

Fattahi, S., Amjadi-Moheb, F., Tabaripour, R., Ashrafi, G. H., & Akhavan-Niaki, H. (2020). PI3K/AKT/mTOR signaling in gastric cancer: Epigenetics and beyond. *Life Sci, 262*, 118513. doi:10.1016/j.lfs.2020.118513

Feng, J., Tang, D., Wang, J., Zhou, Q., Peng, J., Lou, H., . . . Zou, J. (2022). SHR-1701, a bifunctional fusion protein targeting PD-L1 and TGF-β, for recurrent or metastatic cervical cancer: a clinical expansion cohort of phase 1 study. *Clin Cancer Res*. doi:10.1158/1078-0432.Ccr-22-0346

Ferlay, J., Ervik, M., Lam, F., Colombet, M., Mery, L., Piñeros, M., . . . Bray, F. (2018). Global cancer observatory: cancer today. *Lyon, France: international agency for research on cancer*, 1-6.

Ferro, A., Costa, A. R., Morais, S., Bertuccio, P., Rota, M., Pelucchi, C., . . . Lunet, N. (2020). Fruits and vegetables intake and gastric cancer risk: A pooled analysis within the Stomach cancer Pooling Project. *International Journal of Cancer, 147*(11), 3090-3101. doi:https://doi.org/10.1002/ijc.33134

Ferro, A., Rosato, V., Rota, M., Costa, A. R., Morais, S., Pelucchi, C., . . . Lunet, N. (2020). Meat intake and risk of gastric cancer in the Stomach cancer Pooling (StoP) project. *International Journal of Cancer, 147*(1), 45-55. doi:https://doi.org/10.1002/ijc.32707

Flaherty, K. T., Gray, R., Chen, A., Li, S., Patton, D., Hamilton, S. R., . . . Conley, B. A. (2020). The Molecular Analysis for Therapy Choice (NCI-MATCH) Trial: Lessons for Genomic Trial Design. *J Natl Cancer Inst, 112*(10), 1021-1029. doi:10.1093/jnci/djz245

Fortunato, L., & Rushton, L. (2015). Stomach cancer and occupational exposure to asbestos: a meta-analysis of occupational cohort studies. *British Journal of Cancer, 112*(11), 1805-1815. doi:10.1038/bjc.2014.599

Fuchs, C. S., Tomasek, J., Yong, C. J., Dumitru, F., Passalacqua, R., Goswami, C., . . . Tabernero, J. (2014). Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. *The Lancet, 383*(9911), 31-39. doi:10.1016/S0140-6736(13)61719-5

Fujihara, K. M., Corrales Benitez, M., Cabalag, C. S., Zhang, B. Z., Ko, H. S., Liu, D. S., . . . Clemons, N. J. (2021). SLC7A11 Is a Superior Determinant of APR-246 (Eprenetapopt) Response than TP53 Mutation Status. *Mol Cancer Ther, 20*(10), 1858-1867. doi:10.1158/1535-7163.Mct-21-0067

Gall, V. A., Philips, A. V., Qiao, N., Clise-Dwyer, K., Perakis, A. A., Zhang, M., . . . Mittendorf, E. A. (2017). Trastuzumab Increases HER2 Uptake and Cross-Presentation by Dendritic Cells. *Cancer Res, 77*(19), 5374-5383. doi:10.1158/0008-5472.Can-16-2774

Ghosh, C., Luong, G., & Sun, Y. (2021). A snapshot of the PD-1/PD-L1 pathway. *Journal of Cancer, 12*(9), 2735-2746. doi:10.7150/jca.57334

Goldenberg, D. M., Stein, R., & Sharkey, R. M. (2018). The emergence of trophoblast cell-surface antigen 2 (TROP-2) as a novel cancer target. *Oncotarget, 9*(48), 28989-29006. doi:10.18632/oncotarget.25615

Goyal, L., Borad, M., Subbiah, V., Mahipal, A., Kamath, S., Mody, K., . . . Schram, A. M. (2021). Abstract P02-02: First results of RLY-4008, a potent and highly selective FGFR2 inhibitor in a first-in-human study in patients with FGFR2-altered cholangiocarcinoma and multiple solid tumors. *Molecular Cancer Therapeutics, 20*(12_Supplement), P02-02-P02-02. doi:10.1158/1535-7163.Targ-21-p02-02

Group, F.-N. B. W. (2016, January 7, 2025). BEST (Biomarkers, EndpointS, and other Tools) Resource Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK326791/

Group, t. I. G. C. S. (2013). Randomized clinical trial comparing survival after D1 or D2 gastrectomy for gastric cancer. *British Journal of Surgery, 101*(2), 23-31. doi:10.1002/bjs.9345

Guo, Y., Li, Z.-X., Zhang, J.-Y., Ma, J.-L., Zhang, L., Zhang, Y., . . . You, W.-C. (2020). Association Between Lifestyle Factors, Vitamin and Garlic Supplementation, and Gastric Cancer Outcomes: A Secondary Analysis of a Randomized Clinical Trial. *JAMA Network Open, 3*(6), e206628-e206628. doi:10.1001/jamanetworkopen.2020.6628

Guo, Y., Yuan, C., Ying, J., Zhu, X., Luan, G., Zhang, B., . . . Li, J. (2021). Phase I result of ICP-192 (gunagratinib), a highly selective irreversible FGFR inhibitor, in patients with advanced solid tumors harboring FGFR pathway alterations. *Journal of Clinical Oncology, 39*(15_suppl), 4092-4092. doi:10.1200/JCO.2021.39.15_suppl.4092

Hall, P. S., Swinson, D., Cairns, D. A., Waters, J. S., Petty, R., Allmark, C., . . . Seymour, M. T. (2021). Efficacy of Reduced-Intensity Chemotherapy With Oxaliplatin and Capecitabine on Quality of Life and Cancer Control Among Older and Frail Patients With Advanced Gastroesophageal Cancer: The GO2 Phase 3 Randomized Clinical Trial. *JAMA Oncol, 7*(6), 869-877. doi:10.1001/jamaoncol.2021.0848

Hamadani, M., Collins, G. P., Caimi, P. F., Samaniego, F., Spira, A., Davies, A., . . . Horwitz, S. (2021). Camidanlumab tesirine in patients with relapsed or refractory lymphoma: a phase 1, open-label, multicentre, dose-escalation, dose-expansion study. *Lancet Haematol, 8*(6), e433-e445. doi:10.1016/s2352-3026(21)00103-4

Hamashima, C., Ogoshi, K., Okamoto, M., Shabana, M., Kishimoto, T., & Fukao, A. (2013). A Community-Based, Case-Control Study Evaluating Mortality Reduction from Gastric Cancer by Endoscopic Screening in Japan. *PLOS ONE, 8*(11), e79088. doi:10.1371/journal.pone.0079088

Han, Y., Chen, M. K., Wang, H. L., Hsu, J. L., Li, C. W., Chu, Y. Y., . . . Hung, M. C. (2019). Synergism of PARP inhibitor fluzoparib (HS10160) and MET inhibitor HS10241 in breast and ovarian cancer cells. *Am J Cancer Res, 9*(3), 608-618.

Hauptmann, M., Fossa, S. D., Stovall, M., van Leeuwen, F. E., Johannesen, T. B., Rajaraman, P., . . . Morton, L. M. (2015). Increased stomach cancer risk following radiotherapy for testicular cancer. *British Journal of Cancer, 112*(1), 44-51. doi:10.1038/bjc.2014.552

Henderson, T. O., Oeffinger, K. C., Whitton, J., Leisenring, W., Neglia, J., Meadows, A., . . . Nathan, P. C. (2012). Secondary Gastrointestinal Cancer in Childhood Cancer Survivors. *Annals of Internal Medicine, 156*(11), 757-766. doi:10.7326/0003-4819-156-11-201206050-00002

Hescheler, D. A., Hartmann, M. J. M., Riemann, B., Michel, M., Bruns, C. J., Alakus, H., & Chiapponi, C. (2022). Anaplastic thyroid cancer: genome-based search for new

targeted therapy options. *Endocrine Connections*, EC-21-0624. doi:10.1530/ec-21-0624
Hescheler, D. A., Plum, P. S., Zander, T., Quaas, A., Korenkov, M., Gassa, A., . . . Alakus, H. (2020). Identification of targeted therapy options for gastric adenocarcinoma by comprehensive analysis of genomic data. *Gastric cancer : official journal of the International Gastric Cancer Association and the Japanese Gastric Cancer Association, 23*(4), 627-638. doi:10.1007/s10120-020-01045-9
Hinner, M. J., Aiba, R. S. B., Jaquin, T. J., Berger, S., Dürr, M. C., Schlosser, C., . . . Olwill, S. A. (2019). Tumor-Localized Costimulatory T-Cell Engagement by the 4-1BB/HER2 Bispecific Antibody-Anticalin Fusion PRS-343. *Clin Cancer Res, 25*(19), 5878-5889. doi:10.1158/1078-0432.Ccr-18-3654
Howson, C. P., Tomohiko, H., & Wynder, E. L. (1986). The decline in gastric cancer: Epidemiology of an unplanned triumph. *Epidemiologic Reviews, 8*(1), 1-27. doi:10.1093/oxfordjournals.epirev.a036288
Hu, B., El Hajj, N., Sittler, S., Lammert, N., Barnes, R., & Meloni-Ehrig, A. (2012). Gastric cancer: Classification, histology and application of molecular pathology. *Journal of gastrointestinal oncology, 3*(3), 251-261. doi:10.3978/j.issn.2078-6891.2012.021
Hua, H., Kong, Q., Zhang, H., Wang, J., Luo, T., & Jiang, Y. (2019). Targeting mTOR for cancer therapy. *J Hematol Oncol, 12*(1), 71. doi:10.1186/s13045-019-0754-1
Huang, J., Mo, H., Zhang, W., Chen, X., Qu, D., Wang, X., . . . Xu, B. (2019). Promising efficacy of SHR-1210, a novel anti-programmed cell death 1 antibody, in patients with advanced gastric and gastroesophageal junction cancer in China. *Cancer, 125*(5), 742-749. doi:10.1002/cncr.31855
Hwang, S. W., Lee, D. H., Lee, S. H., Park, Y. S., Hwang, J. H., Kim, J. W., . . . Song, I. S. (2010). Preoperative staging of gastric cancer by endoscopic ultrasonography and multidetector-row computed tomography. *J Gastroenterol Hepatol, 25*(3), 512-518. doi:10.1111/j.1440-1746.2009.06106.x
In, H., Solsky, I., Palis, B., Langdon-Embry, M., Ajani, J., & Sano, T. (2017). Validation of the 8th Edition of the AJCC TNM Staging System for Gastric Cancer using the National Cancer Database. *Annals of Surgical Oncology, 24*(12), 3683-3691. doi:10.1245/s10434-017-6078-x
Inoue, K., Tobe, T., Kan, N., Nio, Y., Sakai, M., Takeuchi, E., & Sugiyama, T. (1991). Problems in the definition and treatment of early gastric cancer. *Br J Surg, 78*(7), 818-821. doi:10.1002/bjs.1800780717
Ishaq, S., & Nunn, L. (2015). Helicobacter pylori and gastric cancer: a state of the art review. *Gastroenterology and hepatology from bed to bench, 8*(Suppl 1), S6-S14. Retrieved from https://pubmed.ncbi.nlm.nih.gov/26171139
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4495426/
Issafras, H., Fan, S., Tseng, C. L., Cheng, Y., Lin, P., Xiao, L., . . . Jiang, W. (2021). Structural basis of HLX10 PD-1 receptor recognition, a promising anti-PD-1 antibody clinical candidate for cancer immunotherapy. *PLOS ONE, 16*(12), e0257972. doi:10.1371/journal.pone.0257972
Janjigian, Y. Y., Kawazoe, A., Yañez, P., Li, N., Lonardi, S., Kolesnik, O., . . . Chung, H. C. (2021). The KEYNOTE-811 trial of dual PD-1 and HER2 blockade in HER2-positive gastric cancer. *Nature, 600*(7890), 727-730. doi:10.1038/s41586-021-04161-3
Javle, M. M., Abou-Alfa, G. K., Macarulla, T., Personeni, N., Adeva, J., Bergamo, F., . . . Borad, M. J. (2022). Efficacy of derazantinib in intrahepatic cholangiocarcinoma patients with FGFR2 mutations or amplifications: Interim results from the phase 2 study FIDES-01. *Journal of Clinical Oncology, 40*(4_suppl), 427-427. doi:10.1200/JCO.2022.40.4_suppl.427
Jiang, C., Zhang, L., Xu, X., Qi, M., Zhang, J., He, S., . . . Song, S. (2021). Engineering a Smart Agent for Enhanced Immunotherapy Effect by Simultaneously Blocking PD-L1 and CTLA-4. *Adv Sci (Weinh), 8*(20), e2102500. doi:10.1002/advs.202102500
Jiang, H., Zheng, Y., Qian, J., Mao, C., Xu, X., Li, N., . . . Xu, N. (2020). Safety and efficacy of sintilimab combined with oxaliplatin/capecitabine as first-line treatment in patients with

locally advanced or metastatic gastric/gastroesophageal junction adenocarcinoma in a phase Ib clinical trial. *BMC Cancer, 20*(1), 760. doi:10.1186/s12885-020-07251-z
Joo, W. D., Visintin, I., & Mor, G. (2013). Targeted cancer therapy--are the days of systemic chemotherapy numbered? *Maturitas, 76*(4), 308-314. doi:10.1016/J.MATURITAS.2013.09.008
Joshi, S. S., & Badgwell, B. D. (2021). Current treatment and recent progress in gastric cancer. *CA: A Cancer Journal for Clinicians, 71*(3), 264-279. doi:https://doi.org/10.3322/caac.21657
Jung, M., Park, K. H., Kim, H. M., Kim, T. S., Zhang, X., Park, S. M., . . . Rha, S. Y. (2019). Inhibiting casein kinase 2 overcomes paclitaxel resistance in gastric cancer. *Gastric Cancer, 22*(6), 1153-1163. doi:10.1007/s10120-019-00971-7
Jung, S. Y., Hwang, S., Clarke, J. M., Bauer, T. M., Keedy, V. L., Lee, H., . . . Lee, J. I. (2020). Pharmacokinetic characteristics of vactosertib, a new activin receptor-like kinase 5 inhibitor, in patients with advanced solid tumors in a first-in-human phase 1 study. *Invest New Drugs, 38*(3), 812-820. doi:10.1007/s10637-019-00835-y
Kamangar, F., Cheng, C., Abnet, C. C., & Rabkin, C. S. (2006). Interleukin-1B Polymorphisms and Gastric Cancer Risk—A Meta-analysis. *Cancer Epidemiology, Biomarkers & Prevention, 15*(10), 1920-1928. doi:10.1158/1055-9965.Epi-06-0267
Kanehisa Laboratories. (2022). Kyoto Encyclopedia of Genes and Genomes (KEGG) Pathway database. Retrieved from https://www.genome.jp/kegg/pathway.html
Kanehisa, M. (2000). *Post-genome informatics*. Oxford, UK: Oxford University Press.
Kanehisa, M., & Goto, S. (2000). KEGG: kyoto encyclopedia of genes and genomes. *Nucleic Acids Res, 28*(1), 27-30. doi:10.1093/nar/28.1.27
Karimi, P., Islami, F., Anandasabapathy, S., Freedman, N. D., & Kamangar, F. (2014). Gastric Cancer: Descriptive Epidemiology, Risk Factors, Screening, and Prevention. *Cancer Epidemiology, Biomarkers & Prevention, 23*(5), 700-713. doi:10.1158/1055-9965.Epi-13-1057
Katoh, M., Loriot, Y., Nakayama, I., Hamada, A., Shitara, K., & Katoh, M. (2025). Antibody-drug conjugates targeting the cadherin, claudin and nectin families of adhesion molecules. *Front Mol Med, 5*, 1661016. doi:10.3389/fmmed.2025.1661016
Katzka, D. A., & Kahrilas, P. J. (2020). Advances in the diagnosis and management of gastroesophageal reflux disease. *BMJ, 371*, m3786. doi:10.1136/bmj.m3786
Keam, B., Ock, C. Y., Kim, T. M., Oh, D. Y., Kang, W. K., Park, Y. H., . . . Park, Y. S. (2021). A phase I study of IMC-001, a PD-L1 blocker, in patients with metastatic or locally advanced solid tumors. *Invest New Drugs, 39*(6), 1624-1632. doi:10.1007/s10637-021-01078-6
KEGG. (2022). KEGG pathways in cancer Retrieved from https://www.kegg.jp/pathway/hsa05200
Khongorzul, P., Ling, C. J., Khan, F. U., Ihsan, A. U., & Zhang, J. (2020). Antibody-Drug Conjugates: A Comprehensive Review. *Mol Cancer Res, 18*(1), 3-19. doi:10.1158/1541-7786.Mcr-19-0582
Kim, H., Hwang, Y., Sung, H., Jang, J., Ahn, C., Kim, S. G., . . . Park, S. K. (2018). Effectiveness of Gastric Cancer Screening on Gastric Cancer Incidence and Mortality in a Community-Based Prospective Cohort. *Cancer Res Treat, 50*(2), 582-589. doi:10.4143/crt.2017.048
Kim, M. A., Lee, H. S., Lee, H. E., Jeon, Y. K., Yang, H. K., & Kim, W. H. (2008). EGFR in gastric carcinomas: prognostic significance of protein overexpression and high gene copy number. *Histopathology, 52*(6), 738-746. doi:10.1111/j.1365-2559.2008.03021.x
Kim, T. M., Lee, K. W., Oh, D. Y., Lee, J. S., Im, S. A., Kim, D. W., . . . Bang, Y. J. (2018). Phase 1 Studies of Poziotinib, an Irreversible Pan-HER Tyrosine Kinase Inhibitor in Patients with Advanced Solid Tumors. *Cancer Res Treat, 50*(3), 835-842. doi:10.4143/crt.2017.303
Klempner, S. J., Bendell, J. C., Villaflor, V. M., Tenner, L. L., Stein, S. M., Rottman, J. B., . . . Strickler, J. H. (2021). Safety, Efficacy, and Biomarker Results from a Phase Ib Study of the Anti-DKK1 Antibody DKN-01 in Combination with Pembrolizumab in Advanced

Esophagogastric Cancers. *Mol Cancer Ther, 20*(11), 2240-2249. doi:10.1158/1535-7163.Mct-21-0273
Knödler, M., Körfer, J., Kunzmann, V., Trojan, J., Daum, S., Schenk, M., . . . Lordick, F. (2018). Randomised phase II trial to investigate catumaxomab (anti-EpCAM × anti-CD3) for treatment of peritoneal carcinomatosis in patients with gastric cancer. *Br J Cancer, 119*(3), 296-302. doi:10.1038/s41416-018-0150-6
Kumar, S., Metz, D. C., Ellenberg, S., Kaplan, D. E., & Goldberg, D. S. (2020). Risk Factors and Incidence of Gastric Cancer After Detection of Helicobacter pylori Infection: A Large Cohort Study. *Gastroenterology, 158*(3), 527-536.e527. doi:https://doi.org/10.1053/j.gastro.2019.10.019
Kundu, P., Das, S., & Chattopadhyay, N. (2019). Managing efficacy and toxicity of drugs: Targeted delivery and excretion. *Int J Pharm, 565*, 378-390. doi:10.1016/j.ijpharm.2019.04.058
Kwon, M., Kim, G., Kim, R., Kim, K. T., Kim, S. T., Smith, S., . . . Lee, J. (2022). Phase II study of ceralasertib (AZD6738) in combination with durvalumab in patients with advanced gastric cancer. *J Immunother Cancer, 10*(7). doi:10.1136/jitc-2022-005041
Ladeiras-Lopes, R., Pereira, A. K., Nogueira, A., Pinheiro-Torres, T., Pinto, I., Santos-Pereira, R., & Lunet, N. (2008). Smoking and gastric cancer: systematic review and meta-analysis of cohort studies. *Cancer Causes & Control, 19*(7), 689-701. doi:10.1007/s10552-008-9132-y
Le Joncour, V., Martins, A., Puhka, M., Isola, J., Salmikangas, M., Laakkonen, P., . . . Barok, M. (2019). A Novel Anti-HER2 Antibody-Drug Conjugate XMT-1522 for HER2-Positive Breast and Gastric Cancers Resistant to Trastuzumab Emtansine. *Mol Cancer Ther, 18*(10), 1721-1730. doi:10.1158/1535-7163.Mct-19-0207
Lee, H. J., Hyung, W. J., Yang, H. K., Han, S. U., Park, Y. K., An, J. Y., . . . Kim, M. C. (2019). Short-term Outcomes of a Multicenter Randomized Controlled Trial Comparing Laparoscopic Distal Gastrectomy With D2 Lymphadenectomy to Open Distal Gastrectomy for Locally Advanced Gastric Cancer (KLASS-02-RCT). *Ann Surg, 270*(6), 983-991. doi:10.1097/sla.0000000000003217
Lee, J., Lim, D. H., Kim, S., Park, S. H., Park, J. O., Park, Y. S., . . . Kang, W. K. (2012). Phase III trial comparing capecitabine plus cisplatin versus capecitabine plus cisplatin with concurrent capecitabine radiotherapy in completely resected gastric cancer with D2 lymph node dissection: the ARTIST trial. *J Clin Oncol, 30*(3), 268-273. doi:10.1200/jco.2011.39.1953
Lee, J.-S. (2026). Evolving Molecular Subtypes of Gastric Cancer: From Past Classifications to Present Consensus and Future Directions for Precision Therapy. *J Gastric Cancer, 26*(1), 16-30. Retrieved from https://doi.org/10.5230/jgc.2026.26.e12
Lee, M. X., Wong, A. L. A., Ow, S., Sundar, R., Tan, D. S. P., Soo, R. A., . . . Lee, S. C. (2022). Phase Ib Dose-Finding Study of Varlitinib Combined with Weekly Paclitaxel With or Without Carboplatin ± Trastuzumab in Advanced Solid Tumors. *Target Oncol, 17*(2), 141-151. doi:10.1007/s11523-022-00867-0
Lee, S. S., Chung, H. Y., Kwon, O. K., & Yu, W. (2016). Long-term Quality of Life After Distal Subtotal and Total Gastrectomy: Symptom- and Behavior-oriented Consequences. *Ann Surg, 263*(4), 738-744. doi:10.1097/sla.0000000000001481
Lee, T. S., Kim, J. Y., Lee, M. H., Cho, I. R., Paik, W. H., Ryu, J. K., . . . Lee, S. H. (2023). Savolitinib: A Promising Targeting Agent for Cancer. *Cancers (Basel), 15*(19). doi:10.3390/cancers15194708
Lee, W., Ahn, Y.-S., Lee, S., Song, B. M., Hong, S., & Yoon, J.-H. (2016). Occupational exposure to crystalline silica and gastric cancer: a systematic review and meta-analysis. *Occupational and Environmental Medicine, 73*(11), 794-801. doi:10.1136/oemed-2016-103552
Lee, Y. T., Tan, Y. J., & Oon, C. E. (2018). Molecular targeted therapy: Treating cancer with specificity. *Eur J Pharmacol, 834*, 188-196. doi:10.1016/j.ejphar.2018.07.034
Leong, T., Smithers, B. M., Haustermans, K., Michael, M., Gebski, V., Miller, D., . . . Wong, R. (2017). TOPGEAR: A Randomized, Phase III Trial of Perioperative ECF Chemotherapy

with or Without Preoperative Chemoradiation for Resectable Gastric Cancer: Interim Results from an International, Intergroup Trial of the AGITG, TROG, EORTC and CCTG. *Ann Surg Oncol, 24*(8), 2252-2258. doi:10.1245/s10434-017-5830-6

Li, G., Zhu, L., Cao, Z., Wang, J., Zhou, F., Wang, X., . . . Nie, G. (2018). A New Participant in the Pathogenesis of Alcoholic Gastritis: Pyroptosis. *Cellular Physiology and Biochemistry, 49*(1), 406-418. doi:10.1159/000492902

Li, H., Zhang, X., Xu, Z., Li, L., Liu, W., Dai, Z., . . . Hu, C. (2021). Preclinical evaluation of MRG002, a novel HER2-targeting antibody-drug conjugate with potent antitumor activity against HER2-positive solid tumors. *Antib Ther, 4*(3), 175-184. doi:10.1093/abt/tbab017

Li, J., Deng, Y., Zhang, W., Zhou, A. P., Guo, W., Yang, J., . . . Shen, L. (2021). Subcutaneous envafolimab monotherapy in patients with advanced defective mismatch repair/microsatellite instability high solid tumors. *J Hematol Oncol, 14*(1), 95. doi:10.1186/s13045-021-01095-1

Li, J., Woods, Susan L., Healey, S., Beesley, J., Chen, X., Lee, Jason S., . . . Chenevix-Trench, G. (2016). Point Mutations in Exon 1B of APC Reveal Gastric Adenocarcinoma and Proximal Polyposis of the Stomach as a Familial Adenomatous Polyposis Variant. *The American Journal of Human Genetics, 98*(5), 830-842. doi:https://doi.org/10.1016/j.ajhg.2016.03.001

Li, L., Tang, P., Li, S., Qin, X., Yang, H., Wu, C., & Liu, Y. (2017). Notch signaling pathway networks in cancer metastasis: a new target for cancer therapy. *Med Oncol, 34*(10), 180. doi:10.1007/s12032-017-1039-6

Li, N., Bu, H., Liu, J., Zhu, J., Zhou, Q., Wang, L., . . . Wu, L. (2021). An Open-label, Multicenter, Single-arm, Phase II Study of Fluzoparib in Patients with Germline BRCA1/2 Mutation and Platinum-sensitive Recurrent Ovarian Cancer. *Clin Cancer Res, 27*(9), 2452-2458. doi:10.1158/1078-0432.Ccr-20-3546

Li, Q., Liu, M., Sun, Y., Jin, T., Zhu, P., Wan, X., . . . Tu, G. (2021). SLC6A8-mediated intracellular creatine accumulation enhances hypoxic breast cancer cell survival via ameliorating oxidative stress. *Journal of Experimental & Clinical Cancer Research, 40*(1), 168. doi:10.1186/s13046-021-01933-7

Li, R., Li, J., Wang, Y., Liu, X., Xu, W., Sun, R., . . . Jiang, J. (2025). The artificial intelligence revolution in gastric cancer management: clinical applications. *Cancer Cell Int, 25*(1), 111. doi:10.1186/s12935-025-03756-4

Li, X., You, J., Hong, L., Liu, W., Guo, P., & Hao, X. (2023). Neoantigen cancer vaccines: a new star on the horizon. *Cancer biology & medicine, 21*(4), 274-311. doi:10.20892/j.issn.2095-3941.2023.0395

Li, Z., Bai, B., Xie, F., & Zhao, Q. (2018). Distal versus total gastrectomy for middle and lower-third gastric cancer: A systematic review and meta-analysis. *International Journal of Surgery, 53*, 163-170. doi:https://doi.org/10.1016/j.ijsu.2018.03.047

Liu, J., Gao, T., Tan, Z., Li, S., Xu, J., Bai, C., . . . Guo, W. (2022). Phase II study of TQB2450, a novel PD-L1 antibody, in combination with anlotinib in patients with locally advanced or metastatic soft tissue sarcoma. *Clin Cancer Res*. doi:10.1158/1078-0432.Ccr-22-0871

Liu, Q., Chu, Y., Shao, J., Qian, H., Yang, J., Sha, H., . . . Liu, B. (2022). Benefits of an Immunogenic Personalized Neoantigen Nanovaccine in Patients with High-Risk Gastric/Gastroesophageal Junction Cancer. *Adv Sci (Weinh), 10*(1), e2203298. doi:10.1002/advs.202203298

Liu, Y., Lian, W., Zhao, X., Diao, Y., Xu, J., Xiao, L., . . . Wang, J. (2020). SKB264 ADC: A first-in-human study of SKB264 in patients with locally advanced unresectable/metastatic solid tumors who are refractory to available standard therapies. *Journal of Clinical Oncology, 38*(15_suppl), TPS3659-TPS3659. doi:10.1200/JCO.2020.38.15_suppl.TPS3659

Lombardo, F., Aiolfi, A., Cavalli, M., Mini, E., Lastraioli, C., Panizzo, V., . . . Bona, D. (2022). Techniques for reconstruction after distal gastrectomy for cancer: updated network

meta-analysis of randomized controlled trials. *Langenbeck's Archives of Surgery, 407*(1), 75-86. doi:10.1007/s00423-021-02411-6

Long, G. V., Dummer, R., Hamid, O., Gajewski, T. F., Caglevic, C., Dalle, S., . . . Mitchell, T. C. (2019). Epacadostat plus pembrolizumab versus placebo plus pembrolizumab in patients with unresectable or metastatic melanoma (ECHO-301/KEYNOTE-252): a phase 3, randomised, double-blind study. *Lancet Oncol, 20*(8), 1083-1097. doi:10.1016/s1470-2045(19)30274-8

Lordick, F., Carneiro, F., Cascinu, S., Fleitas, T., Haustermans, K., Piessen, G., . . . Smyth, E. C. (2022). Gastric cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Annals of Oncology, 33*(10), 1005-1020. doi:10.1016/j.annonc.2022.07.004

Lordick, F., Kang, Y. K., Chung, H. C., Salman, P., Oh, S. C., Bodoky, G., . . . Moehler, M. (2013). Capecitabine and cisplatin with or without cetuximab for patients with previously untreated advanced gastric cancer (EXPAND): a randomised, open-label phase 3 trial. *Lancet Oncol, 14*(6), 490-499. doi:10.1016/s1470-2045(13)70102-5

Luo, J., Dai, X., Hu, H., Chen, J., Zhao, L., Yang, C., . . . Wang, P. (2020). Fluzoparib increases radiation sensitivity of non-small cell lung cancer (NSCLC) cells without BRCA1/2 mutation, a novel PARP1 inhibitor undergoing clinical trials. *J Cancer Res Clin Oncol, 146*(3), 721-737. doi:10.1007/s00432-019-03097-6

Lyons, K., Le, L. C., Pham, Y. T.-H., Borron, C., Park, J. Y., Tran, C. T. D., . . . Luu, H. N. (2019). Gastric cancer: epidemiology, biology, and prevention: a mini review. *European Journal of Cancer Prevention, 28*(5), 397-412. doi:10.1097/cej.0000000000000480

Ma, K., Baloch, Z., He, T. T., & Xia, X. (2017). Alcohol Consumption and Gastric Cancer Risk: A Meta-Analysis. *Med Sci Monit, 23*, 238-246. doi:10.12659/msm.899423

Macdonald, J. S., Smalley, S. R., Benedetti, J., Hundahl, S. A., Estes, N. C., Stemmermann, G. N., . . . Martenson, J. A. (2001). Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med, 345*(10), 725-730. doi:10.1056/NEJMoa010187

Machlowska, J., Baj, J., Sitarz, M., Maciejewski, R., & Sitarz, R. (2020). Gastric Cancer: Epidemiology, Risk Factors, Classification, Genomic Characteristics and Treatment Strategies. *Int J Mol Sci, 21*(11). doi:10.3390/ijms21114012

Mantovani, F., Collavin, L., & Del Sal, G. (2019). Mutant p53 as a guardian of the cancer cell. *Cell Death Differ, 26*(2), 199-212. doi:10.1038/s41418-018-0246-9

Marcus, L., Fashoyin-Aje, L. A., Donoghue, M., Yuan, M., Rodriguez, L., Gallagher, P. S., . . . Lemery, S. J. (2021). FDA Approval Summary: Pembrolizumab for the Treatment of Tumor Mutational Burden-High Solid Tumors. *Clin Cancer Res, 27*(17), 4685-4689. doi:10.1158/1078-0432.Ccr-21-0327

Markham, A. (2021). Savolitinib: First Approval. *Drugs, 81*(14), 1665-1670. doi:10.1007/s40265-021-01584-0

Marofi, F., Motavalli, R., Safonov, V. A., Thangavelu, L., Yumashev, A. V., Alexander, M., . . . Khiavi, F. M. (2021). CAR T cells in solid tumors: challenges and opportunities. *Stem Cell Res Ther, 12*(1), 81. doi:10.1186/s13287-020-02128-1

Mateo, J., Ganji, G., Lemech, C., Burris, H. A., Han, S. W., Swales, K., . . . Arkenau, H. T. (2017). A First-Time-in-Human Study of GSK2636771, a Phosphoinositide 3 Kinase Beta-Selective Inhibitor, in Patients with Advanced Solid Tumors. *Clin Cancer Res, 23*(19), 5981-5992. doi:10.1158/1078-0432.Ccr-17-0725

Medicine, U. S. N. L. o. (2022). [Clinicaltrials.gov].

Mencel, J., Slater, S., Cartwright, E., & Starling, N. (2022). The Role of ctDNA in Gastric Cancer. *Cancers (Basel), 14*(20). doi:10.3390/cancers14205105

Mendelsohn, J., Gray, J. W., Howley, P. M., Israel, M. A., & Thompson, C. B. (2014). *The Molecular Basis of Cancer* (4 ed.): Elsevier Inc.

Meric-Bernstam, F., Bahleda, R., Hierro, C., Sanson, M., Bridgewater, J., Arkenau, H. T., . . . Goyal, L. (2022). Futibatinib, an Irreversible FGFR1-4 Inhibitor, in Patients with Advanced Solid Tumors Harboring FGF/FGFR Aberrations: A Phase I Dose-Expansion Study. *Cancer Discov, 12*(2), 402-415. doi:10.1158/2159-8290.Cd-21-0697

Mohan, V., Das, A., & Sagi, I. (2020). Emerging roles of ECM remodeling processes in cancer. *Semin Cancer Biol, 62*, 192-200. doi:10.1016/j.semcancer.2019.09.004

Mondal, K., Song, C., Tian, J., Ho, C., Rivera, L. B., Huang, J., . . . Stone, G. W. (2021). Abstract LB156: Preclinical evaluation of NGM707, a novel anti-ILT2/anti-ILT4 dual antagonist monoclonal antibody. *Cancer Research, 81*(13_Supplement), LB156-LB156. doi:10.1158/1538-7445.Am2021-lb156

Moore, A. R., Rosenberg, S. C., McCormick, F., & Malek, S. (2020). RAS-targeted therapies: is the undruggable drugged? *Nature reviews. Drug discovery, 19*(8), 533-552. doi:10.1038/s41573-020-0068-6

Morales-Kastresana, A., Siegemund, M., Haak, S., Peper-Gabriel, J., Neiens, V., & Rothe, C. (2022). Anticalin®-based therapeutics: Expanding new frontiers in drug development. *Int Rev Cell Mol Biol, 369*, 89-106. doi:10.1016/bs.ircmb.2022.03.009

Morton, L. M., Dores, G. M., Curtis, R. E., Lynch, C. F., Stovall, M., Hall, P., . . . Leeuwen, F. E. v. (2013). Stomach Cancer Risk After Treatment for Hodgkin Lymphoma. *Journal of Clinical Oncology, 31*(27), 3369-3377. doi:10.1200/jco.2013.50.6832

Moy, R. H., Greally, M., Chou, J. F., Li, J., Desai, A. M., Chalasani, S. B., . . . Ku, G. Y. (2022). Phase I/Ib study of crenolanib with ramucirumab and paclitaxel as second-line therapy for advanced esophagogastric adenocarcinoma. *Cancer Chemother Pharmacol, 89*(2), 255-265. doi:10.1007/s00280-021-04384-1

Mukaisho, K.-i., Nakayama, T., Hagiwara, T., Hattori, T., & Sugihara, H. (2015). Two distinct etiologies of gastric cardia adenocarcinoma: interactions among pH, Helicobacter pylori, and bile acids. *Frontiers in Microbiology, 6*. doi:10.3389/fmicb.2015.00412

Murakami, T. (1971). Pathomorphological diagnosis, definition and gross classification of early gastric cancer. *Gann Monogr Cancer Res, 11*, 53-55. doi:10.1007/bf01654788

Muro, K., Van Cutsem, E., Narita, Y., Pentheroudakis, G., Baba, E., Li, J., . . . Douillard, J. Y. (2019). Pan-Asian adapted ESMO Clinical Practice Guidelines for the management of patients with metastatic gastric cancer: a JSMO-ESMO initiative endorsed by CSCO, KSMO, MOS, SSO and TOS. *Ann Oncol, 30*(1), 19-33. doi:10.1093/annonc/mdy502

Murphy, G., Pfeiffer, R., Camargo, M. C., & Rabkin, C. S. (2009). Meta-analysis Shows That Prevalence of Epstein–Barr Virus-Positive Gastric Cancer Differs Based on Sex and Anatomic Location. *Gastroenterology, 137*(3), 824-833. doi:https://doi.org/10.1053/j.gastro.2009.05.001

Nagtegaal, I. D., Odze, R. D., Klimstra, D., Paradis, V., Rugge, M., Schirmacher, P., . . . Board, t. W. C. o. T. E. (2020). The 2019 WHO classification of tumours of the digestive system. *Histopathology, 76*(2), 182-188. doi:https://doi.org/10.1111/his.13975

Naing, A., Gainor, J. F., Gelderblom, H., Forde, P. M., Butler, M. O., Lin, C. C., . . . Bauer, T. M. (2020). A first-in-human phase 1 dose escalation study of spartalizumab (PDR001), an anti-PD-1 antibody, in patients with advanced solid tumors. *J Immunother Cancer, 8*(1). doi:10.1136/jitc-2020-000530

National Cancer Institute. (2026, 2026, February 9). Targeted Therapy Directed by Genetic Testing in Treating Patients With Locally Advanced or Advanced Solid Tumors, The ComboMATCH Screening Trial. Retrieved from https://clinicaltrials.gov/study/NCT05564377

National Institute of Health. (2022). National Institute of Health homepage. Retrieved from https://www.nih.gov/

National Library of Medicine. About National Center for Biotechnology Information. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/about/intro/

National Library of Medicine. (2022). National Library of Medicine homepage. Retrieved from https://www.nlm.nih.gov/

Naum, C., Bîrlă, R., Marica, D. C., & Constantinoiu, S. (2020). In Search of the Optimal Reconstruction Method after Total Gastrectomy. Is Roux-en-Y the Best? A Review of the Randomized Clinical Trials. *Chirurgia (Bucur), 115*(1), 12-22. doi:10.21614/chirurgia.115.1.12

Nemunaitis, J., Tong, A. W., Nemunaitis, M., Senzer, N., Phadke, A. P., Bedell, C., . . . Fujiwara, T. (2010). A phase I study of telomerase-specific replication competent oncolytic adenovirus (telomelysin) for various solid tumors. *Mol Ther, 18*(2), 429-434. doi:10.1038/mt.2009.262

Nomura, A., Stemmermann, G. N., Chyou, P.-H., Kato, I., Perez-Perez, G. I., & Blaser, M. J. (1991). Helicobacter pylori Infection and Gastric Carcinoma among Japanese Americans in Hawaii. *New England Journal of Medicine, 325*(16), 1132-1136. doi:10.1056/nejm199110173251604

Nunobe, S., Sasako, M., Saka, M., Fukagawa, T., Katai, H., & Sano, T. (2007). Symptom evaluation of long-term postoperative outcomes after pylorus-preserving gastrectomy for early gastric cancer. *Gastric Cancer, 10*(3), 167-172. doi:10.1007/s10120-007-0434-7

O'Hara, M. H., O'Reilly, E. M., Varadhachary, G., Wolff, R. A., Wainberg, Z. A., Ko, A. H., . . . Vonderheide, R. H. (2021). CD40 agonistic monoclonal antibody APX005M (sotigalimab) and chemotherapy, with or without nivolumab, for the treatment of metastatic pancreatic adenocarcinoma: an open-label, multicentre, phase 1b study. *Lancet Oncol, 22*(1), 118-131. doi:10.1016/s1470-2045(20)30532-5

Oh, D. Y., Lee, K. W., Han, S. W., Kim, J. W., Shin, J. W., Jo, S. J., . . . Bang, Y. J. (2019). A First-in-Human Phase I Study of GC1118, a Novel Anti-Epidermal Growth Factor Receptor Antibody, in Patients with Advanced Solid Tumors. *Oncologist, 24*(8), 1037-e1636. doi:10.1634/theoncologist.2019-0294

Ooki, A., Satoh, T., Muro, K., Takashima, A., Kadowaki, S., Sakai, D., . . . Yamaguchi, K. (2022). A phase 1b study of andecaliximab in combination with S-1 plus platinum in Japanese patients with gastric adenocarcinoma. *Sci Rep, 12*(1), 11007. doi:10.1038/s41598-022-13801-1

Owen, K. L., Brockwell, N. K., & Parker, B. S. (2019). JAK-STAT Signaling: A Double-Edged Sword of Immune Regulation and Cancer Progression. *Cancers, 11*(12), 2002. doi:10.3390/cancers11122002

Oya, Y., Hayakawa, Y., & Koike, K. (2020). Tumor microenvironment in gastric cancers. *Cancer Sci, 111*(8), 2696-2707. doi:10.1111/cas.14521

Ozawa, T., Rodriguez, M., Zhao, G., Yao, T. W., Fischer, W.-N., Jandeleit, B., . . . Nicolaides, T. (2021). A Novel Blood-Brain Barrier-Permeable Chemotherapeutic Agent for the Treatment of Glioblastoma. *Cureus, 13*(8), e17595-e17595. doi:10.7759/cureus.17595

Pal, S. K., Tangen, C., Thompson, I. M., Jr., Balzer-Haas, N., George, D. J., Heng, D. Y. C., . . . Lara, P. N., Jr. (2021). A comparison of sunitinib with cabozantinib, crizotinib, and savolitinib for treatment of advanced papillary renal cell carcinoma: a randomised, open-label, phase 2 trial. *Lancet, 397*(10275), 695-703. doi:10.1016/s0140-6736(21)00152-5

Park, D. J., Lee, H. J., Jung, H. C., Kim, W. H., Lee, K. U., & Yang, H. K. (2008). Clinical outcome of pylorus-preserving gastrectomy in gastric cancer in comparison with conventional distal gastrectomy with Billroth I anastomosis. *World J Surg, 32*(6), 1029-1036. doi:10.1007/s00268-007-9441-4

Park, J. E., Jin, M. H., Hur, M., Nam, A.-R., Bang, J.-H., Won, J., . . . Bang, Y.-J. (2019). GC1118, a novel anti-EGFR antibody, has potent KRAS mutation-independent antitumor activity compared with cetuximab in gastric cancer. *Gastric Cancer, 22*(5), 932-940. doi:10.1007/s10120-019-00943-x

Park, S., Chung, H. Y., Lee, S. S., Kwon, O., & Yu, W. (2014). Serial comparisons of quality of life after distal subtotal or total gastrectomy: what are the rational approaches for quality of life management? *J Gastric Cancer, 14*(1), 32-38. doi:10.5230/jgc.2014.14.1.32

Park, S., Jiang, Z., Mortenson, E. D., Deng, L., Radkevich-Brown, O., Yang, X., . . . Fu, Y. X. (2010). The therapeutic effect of anti-HER2/neu antibody depends on both innate and adaptive immunity. *Cancer Cell, 18*(2), 160-170. doi:10.1016/j.ccr.2010.06.014

Parsonnet, J., Friedman, G. D., Vandersteen, D. P., Chang, Y., Vogelman, J. H., Orentreich, N., & Sibley, R. K. (1991). Helicobacter pylori Infection and the Risk of Gastric

Carcinoma. *New England Journal of Medicine, 325*(16), 1127-1131. doi:10.1056/nejm199110173251603
Patel, H. K., & Bihani, T. (2018). Selective estrogen receptor modulators (SERMs) and selective estrogen receptor degraders (SERDs) in cancer treatment. *Pharmacology & Therapeutics, 186*, 1-24. doi:https://doi.org/10.1016/j.pharmthera.2017.12.012
Pauligk, C., Tannapfel, A., Meiler, J., Luley, K. B., Kopp, H.-G., Homann, N., . . . Al-Batran, S.-E. (2015). Pathological response to neoadjuvant 5-FU, oxaliplatin, and docetaxel (FLOT) versus epirubicin, cisplatin, and 5-FU (ECF) in patients with locally advanced, resectable gastric/esophagogastric junction (EGJ) cancer: Data from the phase II part of the FLOT4 phase III study of the AIO. *Journal of Clinical Oncology, 33*(15_suppl), 4016-4016. doi:10.1200/jco.2015.33.15_suppl.4016
Pegram, M. D., Hamilton, E. P., Tan, A. R., Storniolo, A. M., Balic, K., Rosenbaum, A. I., . . . Patel, M. R. (2021). First-in-Human, Phase 1 Dose-Escalation Study of Biparatopic Anti-HER2 Antibody-Drug Conjugate MEDI4276 in Patients with HER2-positive Advanced Breast or Gastric Cancer. *Mol Cancer Ther, 20*(8), 1442-1453. doi:10.1158/1535-7163.Mct-20-0014
Peng, Z., Wei, J., Wang, F., Ying, J., Deng, Y., Gu, K., . . . Shen, L. (2021). Camrelizumab Combined with Chemotherapy Followed by Camrelizumab plus Apatinib as First-line Therapy for Advanced Gastric or Gastroesophageal Junction Adenocarcinoma. *Clin Cancer Res, 27*(11), 3069-3078. doi:10.1158/1078-0432.Ccr-20-4691
Pietrantonio, F., Caporale, M., Morano, F., Scartozzi, M., Gloghini, A., De Vita, F., . . . Di Bartolomeo, M. (2016). HER2 loss in HER2-positive gastric or gastroesophageal cancer after trastuzumab therapy: Implication for further clinical research. *Int J Cancer, 139*(12), 2859-2864. doi:10.1002/ijc.30408
Piro, G., Carbone, C., Cataldo, I., Di Nicolantonio, F., Giacopuzzi, S., Aprile, G., . . . Melisi, D. (2016). An FGFR3 Autocrine Loop Sustains Acquired Resistance to Trastuzumab in Gastric Cancer Patients. *Clin Cancer Res, 22*(24), 6164-6175. doi:10.1158/1078-0432.Ccr-16-0178
Polkowski, W., van Sandick, J. W., Offerhaus, G. J. A., ten Kate, F. J. W., Mulder, J., Obertop, H., & van Lanschot, J. J. B. (1999). Prognostic Value of Laurén Classification and c-erbB-2 Oncogene Overexpression in Adenocarcinoma of the Esophagus and Gastroesophageal Junction. *Annals of Surgical Oncology, 6*(3), 290-297. doi:10.1007/s10434-999-0290-2
Poorolajal, J., Moradi, L., Mohammadi, Y., Cheraghi, Z., & Gohari-Ensaf, F. (2020). Risk factors for stomach cancer: a systematic review and meta-analysis. *Epidemiol Health, 42*(0), e2020004-2020000. doi:10.4178/epih.e2020004
Preston, D. L., Ron, E., Tokuoka, S., Funamoto, S., Nishi, N., Soda, M., . . . Kodama, K. (2007). Solid Cancer Incidence in Atomic Bomb Survivors: 1958–1998. *Radiation Research, 168*(1), 1-64, 64. Retrieved from https://doi.org/10.1667/RR0763.1
PubMed.gov. (2022). About PubMed. Retrieved from https://pubmed.ncbi.nlm.nih.gov/about/
Pusch, F. F., Dorado García, H., Xu, R., Gürgen, D., Bei, Y., Brückner, L., . . . Henssen, A. G. (2024). Elimusertib has Antitumor Activity in Preclinical Patient-Derived Pediatric Solid Tumor Models. *Mol Cancer Ther, 23*(4), 507-519. doi:10.1158/1535-7163.Mct-23-0094
Qi, C., Liu, C., Gong, J., Liu, D., Wang, X., Zhang, P., . . . Shen, L. (2024). Claudin18.2-specific CAR T cells in gastrointestinal cancers: phase 1 trial final results. *Nat Med, 30*(8), 2224-2234. doi:10.1038/s41591-024-03037-z
Qin, Y., Deng, Y., Jiang, H., Hu, N., & Song, B. (2021). Artificial Intelligence in the Imaging of Gastric Cancer: Current Applications and Future Direction. *Front Oncol, 11*, 631686. doi:10.3389/fonc.2021.631686
Raimondi, A., Palermo, F., Prisciandaro, M., Aglietta, M., Antonuzzo, L., Aprile, G., . . . Pietrantonio, F. (2021). TremelImumab and Durvalumab Combination for the Non-OperatIve Management (NOM) of Microsatellite InstabiliTY (MSI)-High Resectable Gastric or Gastroesophageal Junction Cancer: The Multicentre, Single-Arm, Multi-Cohort, Phase II INFINITY Study. *Cancers (Basel), 13*(11). doi:10.3390/cancers13112839

Rawla, P., & Barsouk, A. (2018). Epidemiology of gastric cancer: global trends, risk factors and prevention. *Gastroenterology Review/Przegląd Gastroenterologiczny, 14*(1), 26-38. doi:10.5114/PG.2018.80001

Renehan, A. G., Tyson, M., Egger, M., Heller, R. F., & Zwahlen, M. (2008). Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet, 371*(9612), 569-578. doi:10.1016/s0140-6736(08)60269-x

RKI, R. K. I. U. d. G. d. e. K. i. D. e. V. (2021). *Krebs in Deutschland für 2017/2018*. Retrieved from Berlin: https://www.krebsdaten.de/Krebs/DE/Content/Publikationen/Krebs_in_Deutschland/krebs_in_deutschland_node.html

Roberts, P. J., & Der, C. J. (2007). Targeting the Raf-MEK-ERK mitogen-activated protein kinase cascade for the treatment of cancer. *Oncogene, 26*(22), 3291-3310. doi:10.1038/sj.onc.1210422

Roberts-Thomson, S. J., Chalmers, S. B., & Monteith, G. R. (2019). The Calcium-Signaling Toolkit in Cancer: Remodeling and Targeting. *Cold Spring Harbor perspectives in biology, 11*(8), a035204. doi:10.1101/cshperspect.a035204

Rossi, J. F., Négrier, S., James, N. D., Kocak, I., Hawkins, R., Davis, H., . . . Berns, B. (2010). A phase I/II study of siltuximab (CNTO 328), an anti-interleukin-6 monoclonal antibody, in metastatic renal cell cancer. *Br J Cancer, 103*(8), 1154-1162. doi:10.1038/sj.bjc.6605872

Roviello, G., Catalano, M., Iannone, L. F., Marano, L., Brugia, M., Rossi, G., . . . Antonuzzo, L. (2022). Current status and future perspectives in HER2 positive advanced gastric cancer. *Clinical and Translational Oncology, 24*(6), 981-996. doi:10.1007/s12094-021-02760-0

Sakamoto, H., Yoshimura, K., Saeki, N., Katai, H., Shimoda, T., Matsuno, Y., . . . The Study Group of Millennium Genome Project for, C. (2008). Genetic variation in PSCA is associated with susceptibility to diffuse-type gastric cancer. *Nature Genetics, 40*(6), 730-740. doi:10.1038/ng.152

Sanborn, R. E., Bordoni, R. E., Fleming, G. F., Khasraw, M., Hawthorne, T., Thomas, L. J., . . . Yellin, M. J. (2021). A phase 1 dose-escalation study of a PD-L1xCD27 bispecific antibody CDX-527 in patients with advanced malignancies. *Journal of Clinical Oncology, 39*(15_suppl), 2585-2585. doi:10.1200/JCO.2021.39.15_suppl.2585

Sanchez-Vega, F., Mina, M., Armenia, J., Chatila, W. K., Luna, A., La, K. C., . . . Schultz, N. (2018). Oncogenic Signaling Pathways in The Cancer Genome Atlas. *Cell, 173*(2), 321-337.e310. doi:10.1016/j.cell.2018.03.035

Saragoni, L. (2015). Upgrading the definition of early gastric cancer: better staging means more appropriate treatment. *Cancer biology & medicine, 12*(4), 355-361. doi:10.7497/j.issn.2095-3941.2015.0054

Sarker, D., Dawson, N. A., Aparicio, A. M., Dorff, T. B., Pantuck, A. J., Vaishampayan, U. N., . . . de Bono, J. S. (2021). A Phase I, Open-Label, Dose-Finding Study of GSK2636771, a PI3Kβ Inhibitor, Administered with Enzalutamide in Patients with Metastatic Castration-Resistant Prostate Cancer. *Clin Cancer Res, 27*(19), 5248-5257. doi:10.1158/1078-0432.Ccr-21-1115

Sasaki, M., Chiwaki, F., Kuroda, T., Komatsu, M., Matsusaki, K., Kohno, T., . . . Ogiwara, H. (2020). Efficacy of glutathione inhibitors for the treatment of ARID1A-deficient diffuse-type gastric cancers. *Biochem Biophys Res Commun, 522*(2), 342-347. doi:10.1016/j.bbrc.2019.11.078

Seeneevassen, L., Dubus, P., Gronnier, C., & Varon, C. (2022). Hippo in Gastric Cancer: From Signalling to Therapy. *Cancers (Basel), 14*(9). doi:10.3390/cancers14092282

Semenza, G. L. (2003). Targeting HIF-1 for cancer therapy. *Nature reviews. Cancer, 3*(10), 721-732. doi:10.1038/nrc1187

Seo, S., Ryu, M. H., Park, Y. S., Ahn, J. Y., Park, Y., Park, S. R., . . . Kang, Y. K. (2019). Loss of HER2 positivity after anti-HER2 chemotherapy in HER2-positive gastric cancer

patients: results of the GASTric cancer HER2 reassessment study 3 (GASTHER3). *Gastric Cancer, 22*(3), 527-535. doi:10.1007/s10120-018-0891-1
Sequist, L. V., Han, J. Y., Ahn, M. J., Cho, B. C., Yu, H., Kim, S. W., . . . Oxnard, G. (2020). Osimertinib plus savolitinib in patients with EGFR mutation-positive, MET-amplified, non-small-cell lung cancer after progression on EGFR tyrosine kinase inhibitors: interim results from a multicentre, open-label, phase 1b study. *Lancet Oncol, 21*(3), 373-386. doi:10.1016/s1470-2045(19)30785-5
Shah, M. A., Kennedy, E. B., Alarcon-Rozas, A. E., Alcindor, T., Bartley, A. N., Malowany, A. B., . . . Rajdev, L. (2023). Immunotherapy and Targeted Therapy for Advanced Gastroesophageal Cancer: ASCO Guideline. *J Clin Oncol, 41*(7), 1470-1491. doi:10.1200/jco.22.02331
Shah, M. H., Wei, L., Wirth, L. J., Daniels, G. A., De Souza, J. A., Timmers, C. D., . . . Busaidy, N. L. (2017). Results of randomized phase II trial of dabrafenib versus dabrafenib plus trametinib in BRAF-mutated papillary thyroid carcinoma. *Journal of Clinical Oncology, 35*(15_suppl), 6022-6022. doi:10.1200/jco.2017.35.15_suppl.6022
Shaibu, Z., Chen, Z., Mzee, S. A. S., Theophilus, A., & Danbala, I. A. (2020). Effects of reconstruction techniques after proximal gastrectomy: a systematic review and meta-analysis. *World Journal of Surgical Oncology, 18*(1), 171. doi:10.1186/s12957-020-01936-2
Shannon, P., Markiel, A., Ozier, O., Baliga, N. S., Wang, J. T., Ramage, D., . . . Ideker, T. (2003). Cytoscape: a software environment for integrated models of biomolecular interaction networks. *Genome Res, 13*(11), 2498-2504. doi:10.1101/gr.1239303
Shi, M., Chen, J., Li, K., Fang, Y., Wen, G., Li, X., . . . Feng, J. (2021). SHR-1701, a bifunctional fusion protein targeting PD-L1 and TGF-β, for advanced NSCLC with EGFR mutations: Data from a multicenter phase 1 study. *Journal of Clinical Oncology, 39*(15_suppl), 9055-9055. doi:10.1200/JCO.2021.39.15_suppl.9055
Shi, Y., Hu, Z., Wu, C., Dai, J., Li, H., Dong, J., . . . Shen, H. (2011). A genome-wide association study identifies new susceptibility loci for non-cardia gastric cancer at 3q13.31 and 5p13.1. *Nature Genetics, 43*(12), 1215-1218. doi:10.1038/ng.978
Shibata, D., & Weiss, L. M. (1992). Epstein-Barr virus-associated gastric adenocarcinoma. *Am J Pathol, 140*(4), 769-774.
Shirakawa, Y., Tazawa, H., Tanabe, S., Kanaya, N., Noma, K., Koujima, T., . . . Fujiwara, T. (2021). Phase I dose-escalation study of endoscopic intratumoral injection of OBP-301 (Telomelysin) with radiotherapy in oesophageal cancer patients unfit for standard treatments. *Eur J Cancer, 153*, 98-108. doi:10.1016/j.ejca.2021.04.043
Shirley, M. (2018). Fruquintinib: First Global Approval. *Drugs, 78*(16), 1757-1761. doi:10.1007/s40265-018-0998-z
Shitara, K., Bang, Y. J., Iwasa, S., Sugimoto, N., Ryu, M. H., Sakai, D., . . . Yamaguchi, K. (2020). Trastuzumab Deruxtecan in Previously Treated HER2-Positive Gastric Cancer. *N Engl J Med, 382*(25), 2419-2430. doi:10.1056/NEJMoa2004413
Siewert, J. R., Böttcher, K., Roder, J. D., Busch, R., Hermanek, P., & Meyer, H. J. (1993). Prognostic relevance of systematic lymph node dissection in gastric carcinoma. German Gastric Carcinoma Study Group. *Br J Surg, 80*(8), 1015-1018. doi:10.1002/bjs.1800800829
Skidmore, L., Sakamuri, S., Knudsen, N. A., Hewet, A. G., Milutinovic, S., Barkho, W., . . . Tian, F. (2020). ARX788, a Site-specific Anti-HER2 Antibody-Drug Conjugate, Demonstrates Potent and Selective Activity in HER2-low and T-DM1-resistant Breast and Gastric Cancers. *Mol Cancer Ther, 19*(9), 1833-1843. doi:10.1158/1535-7163.Mct-19-1004
Skoda, A. M., Simovic, D., Karin, V., Kardum, V., Vranic, S., & Serman, L. (2018). The role of the Hedgehog signaling pathway in cancer: A comprehensive review. *Bosnian journal of basic medical sciences, 18*(1), 8-20. doi:10.17305/bjbms.2018.2756
Slagter, A. E., Jansen, E. P. M., van Laarhoven, H. W. M., van Sandick, J. W., van Grieken, N. C. T., Sikorska, K., . . . Verheij, M. (2018). CRITICS-II: a multicentre randomised phase II trial of neo-adjuvant chemotherapy followed by surgery versus neo-adjuvant chemotherapy and subsequent chemoradiotherapy followed by surgery versus neo-

adjuvant chemoradiotherapy followed by surgery in resectable gastric cancer. *BMC Cancer, 18*(1), 877. doi:10.1186/s12885-018-4770-2
Sledge, G. W. (2005). What is targeted therapy? *Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 23*(8), 1614-1615. doi:10.1200/JCO.2005.01.016
Smyth, E. C., Nilsson, M., Grabsch, H. I., van Grieken, N. C. T., & Lordick, F. (2020). Gastric cancer. *The Lancet, 396*(10251), 635-648. doi:https://doi.org/10.1016/S0140-6736(20)31288-5
Smyth, E. C., Verheij, M., Allum, W., Cunningham, D., Cervantes, A., & Arnold, D. (2016). Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up[†]. *Annals of Oncology, 27*, v38-v49. doi:10.1093/annonc/mdw350
Song, M., Chen, X., Wang, L., & Zhang, Y. (2018). Future of anti-PD-1/PD-L1 applications: Combinations with other therapeutic regimens. *Chin J Cancer Res, 30*(2), 157-172. doi:10.21147/j.issn.1000-9604.2018.02.01
Stein, H. J., Sendler, A., & Siewert, J. R. (2002). Site-dependent resection techniques for gastric cancer. *Surgical Oncology Clinics of North America, 11*(2), 405-414. doi:https://doi.org/10.1016/S1055-3207(02)00017-0
Stiekema, J., Trip, A. K., Jansen, E. P., Aarts, M. J., Boot, H., Cats, A., . . . van Sandick, J. W. (2015). Does adjuvant chemoradiotherapy improve the prognosis of gastric cancer after an r1 resection? Results from a dutch cohort study. *Ann Surg Oncol, 22*(2), 581-588. doi:10.1245/s10434-014-4032-8
Sun, K., Jia, K., Lv, H., Wang, S.-Q., Wu, Y., Lei, H., & Chen, X. (2020). EBV-Positive Gastric Cancer: Current Knowledge and Future Perspectives. *Frontiers in Oncology, 10*. doi:10.3389/fonc.2020.583463
Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., & Bray, F. (2021). Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA: A Cancer Journal for Clinicians, 71*(3), 209-249. doi:10.3322/CAAC.21660
Suski, J. M., Braun, M., Strmiska, V., & Sicinski, P. (2021). Targeting cell-cycle machinery in cancer. *Cancer Cell, 39*(6), 759-778. doi:10.1016/j.ccell.2021.03.010
Switzerland Springer Nature. (2022). AdisInsight International. Retrieved from https://adisinsight.springer.com/
Tersmette, A. C., Offerhaus, G. J., Tersmette, K. W., Giardiello, F. M., Moore, G. W., Tytgat, G. N., & Vandenbroucke, J. P. (1990). Meta-analysis of the risk of gastric stump cancer: detection of high risk patient subsets for stomach cancer after remote partial gastrectomy for benign conditions. *Cancer Res, 50*(20), 6486-6489.
The National Cancer Institute. (2022). NCI Drug Dictionary. Retrieved from https://www.cancer.gov/publications/dictionaries/cancer-drug
Thomas, A., Teicher, B. A., & Hassan, R. (2016). Antibody-drug conjugates for cancer therapy. *Lancet Oncol, 17*(6), e254-e262. doi:10.1016/s1470-2045(16)30030-4
Thomas, A., Virdee, P. S., Eatock, M., Lord, S. R., Falk, S., Anthoney, D. A., . . . Middleton, M. R. (2020). Dual Erb B Inhibition in Oesophago-gastric Cancer (DEBIOC): A phase I dose escalating safety study and randomised dose expansion of AZD8931 in combination with oxaliplatin and capecitabine chemotherapy in patients with oesophagogastric adenocarcinoma. *Eur J Cancer, 124*, 131-141. doi:10.1016/j.ejca.2019.10.010
Thura, M., Al-Aidaroos, A. Q., Gupta, A., Chee, C. E., Lee, S. C., Hui, K. M., . . . Zeng, Q. (2019). PRL3-zumab as an immunotherapy to inhibit tumors expressing PRL3 oncoprotein. *Nat Commun, 10*(1), 2484. doi:10.1038/s41467-019-10127-x
Tominaga, N., Gotoda, T., Hara, M., Hale, M. D., Tsuchiya, T., Matsubayashi, J., . . . Grabsch, H. I. (2016). Five biopsy specimens from the proximal part of the tumor reliably determine HER2 protein expression status in gastric cancer. *Gastric cancer : official journal of the International Gastric Cancer Association and the Japanese Gastric Cancer Association, 19*(2), 553-560. doi:10.1007/s10120-015-0502-3

Tramacere, I., Negri, E., Pelucchi, C., Bagnardi, V., Rota, M., Scotti, L., . . . Boffetta, P. (2012). A meta-analysis on alcohol drinking and gastric cancer risk. *Annals of Oncology, 23*(1), 28-36. doi:https://doi.org/10.1093/annonc/mdr135

Triulzi, T., Forte, L., Regondi, V., Di Modica, M., Ghirelli, C., Carcangiu, M. L., . . . Tagliabue, E. (2019). HER2 signaling regulates the tumor immune microenvironment and trastuzumab efficacy. *Oncoimmunology, 8*(1), e1512942. doi:10.1080/2162402x.2018.1512942

Tsimberidou, A. M., Achaval, S. d., Alibhai, I., & Kaseb, A. O. (2021). First-in-man phase I clinical trial evaluating TTI-101, an orally bioavailable, small molecule inhibitor of STAT3, in patients with advanced solid tumors. *Journal of Clinical Oncology, 39*(15_suppl), TPS3158-TPS3158. doi:10.1200/JCO.2021.39.15_suppl.TPS3158

U.S. National Institute of Cancer. (2022). Targeted cancer therapies. Retrieved from https://www.cancer.gov/about-cancer/treatment/types/targeted-therapies/targeted-therapies-fact-sheet

Van Cutsem, E., Bang, Y. J., Mansoor, W., Petty, R. D., Chao, Y., Cunningham, D., . . . Landers, D. (2017). A randomized, open-label study of the efficacy and safety of AZD4547 monotherapy versus paclitaxel for the treatment of advanced gastric adenocarcinoma with FGFR2 polysomy or gene amplification. *Ann Oncol, 28*(6), 1316-1324. doi:10.1093/annonc/mdx107

Van Cutsem, E., Karaszewska, B., Kang, Y. K., Chung, H. C., Shankaran, V., Siena, S., . . . Cunningham, D. (2019). A Multicenter Phase II Study of AMG 337 in Patients with MET-Amplified Gastric/Gastroesophageal Junction/Esophageal Adenocarcinoma and Other MET-Amplified Solid Tumors. *Clin Cancer Res, 25*(8), 2414-2423. doi:10.1158/1078-0432.Ccr-18-1337

van der Wielen, N., Straatman, J., Daams, F., Rosati, R., Parise, P., Weitz, J., . . . van der Peet, D. L. (2021). Open versus minimally invasive total gastrectomy after neoadjuvant chemotherapy: results of a European randomized trial. *Gastric Cancer, 24*(1), 258-271. doi:10.1007/s10120-020-01109-w

Vannella, L., Lahner, E., Osborn, J., & Annibale, B. (2013). Systematic review: gastric cancer incidence in pernicious anaemia. *Alimentary Pharmacology & Therapeutics, 37*(4), 375-382. doi:https://doi.org/10.1111/apt.12177

Vogelstein, B., & Kinzler, K. W. (2004). Cancer genes and the pathways they control. *Nat Med, 10*(8), 789-799. doi:10.1038/nm1087

Waddell, T., Chau, I., Cunningham, D., Gonzalez, D., Okines, A. F., Okines, C., . . . Barbachano, Y. (2013). Epirubicin, oxaliplatin, and capecitabine with or without panitumumab for patients with previously untreated advanced oesophagogastric cancer (REAL3): a randomised, open-label phase 3 trial. *Lancet Oncol, 14*(6), 481-489. doi:10.1016/s1470-2045(13)70096-2

Wainberg, Z. A., Kang, Y. K., Lee, K. W., Qin, S., Yamaguchi, K., Kim, I. H., . . . Enzinger, P. C. (2024). Bemarituzumab as first-line treatment for locally advanced or metastatic gastric/gastroesophageal junction adenocarcinoma: final analysis of the randomized phase 2 FIGHT trial. *Gastric Cancer, 27*(3), 558-570. doi:10.1007/s10120-024-01466-w

Wang, F., Wei, X. L., Wang, F. H., Xu, N., Shen, L., Dai, G. H., . . . Xu, R. H. (2019). Safety, efficacy and tumor mutational burden as a biomarker of overall survival benefit in chemo-refractory gastric cancer treated with toripalimab, a PD-1 antibody in phase Ib/II clinical trial NCT02915432. *Ann Oncol, 30*(9), 1479-1486. doi:10.1093/annonc/mdz197

Wang, J., Xu, X., Wang, T., Guo, Q., Dai, X., Guo, H., . . . Ding, L. (2021). Ceritinib increases sensitivity of AKT inhibitors to gastric cancer. *Eur J Pharmacol, 896*, 173879. doi:10.1016/j.ejphar.2021.173879

Wang, L., Yang, C., Xie, C., Jiang, J., Gao, M., Fu, L., . . . Lou, L. (2019). Pharmacologic characterization of fluzoparib, a novel poly(ADP-ribose) polymerase inhibitor undergoing clinical trials. *Cancer Sci, 110*(3), 1064-1075. doi:10.1111/cas.13947

Wang, L.-D., Zhou, F.-Y., Li, X.-M., Sun, L.-D., Song, X., Jin, Y., . . . Zhang, X.-J. (2010). Genome-wide association study of esophageal squamous cell carcinoma in Chinese

subjects identifies a susceptibility locus at PLCE1. *Nature Genetics, 42*(9), 759-763. doi:10.1038/ng.648
Wang, N., Mei, Q., Wang, Z., Zhao, L., Zhang, D., Liao, D., . . . Kong, F. (2022). Research Progress of Antibody-Drug Conjugate Therapy for Advanced Gastric Cancer. *Front Oncol, 12*, 889017. doi:10.3389/fonc.2022.889017
Wang, S., Dong, D., Zhang, W., Hu, H., Li, H., Zhu, Y., . . . Tian, J. (2021). Specific Borrmann classification in advanced gastric cancer by an ensemble multilayer perceptron network: a multicenter research. *Medical Physics, 48*(9), 5017-5028. doi:https://doi.org/10.1002/mp.15094
Wang, Y., Yuan, X., Li, J., Liu, Z., Li, X., Wang, Z., . . . Wang, X. (2021). The Synergistic Effects of SHR6390 Combined With Pyrotinib on HER2+/HR+ Breast Cancer. *Front Cell Dev Biol, 9*, 785796. doi:10.3389/fcell.2021.785796
Wang, Z. (2017). ErbB Receptors and Cancer. *Methods Mol Biol, 1652*, 3-35. doi:10.1007/978-1-4939-7219-7_1
Wilke, H., Muro, K., Van Cutsem, E., Oh, S. C., Bodoky, G., Shimada, Y., . . . Ohtsu, A. (2014). Ramucirumab 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. *The Lancet Oncology, 15*(11), 1224-1235. doi:10.1016/S1470-2045(14)70420-6
Wishart, D. S., Feunang, Y. D., Guo, A. C., Lo, E. J., Marcu, A., Grant, J. R., . . . Wilson, M. (2018). DrugBank 5.0: a major update to the DrugBank database for 2018. *Nucleic acids research, 46*(D1), D1074-D1082. doi:10.1093/nar/gkx1037
Wong, M. C. S., Huang, J., Chan, P. S. F., Choi, P., Lao, X. Q., Chan, S. M., . . . Liang, P. (2021). Global Incidence and Mortality of Gastric Cancer, 1980-2018. *JAMA Network Open, 4*(7), e2118457-e2118457. doi:10.1001/JAMANETWORKOPEN.2021.18457
Wong, S. H. M., Fang, C. M., Chuah, L. H., Leong, C. O., & Ngai, S. C. (2018). E-cadherin: Its dysregulation in carcinogenesis and clinical implications. *Crit Rev Oncol Hematol, 121*, 11-22. doi:10.1016/j.critrevonc.2017.11.010
Xie, T., Zhang, Z., Zhang, X., Qi, C., Shen, L., & Peng, Z. (2021). Appropriate PD-L1 Cutoff Value for Gastric Cancer Immunotherapy: A Systematic Review and Meta-Analysis. *Frontiers in Oncology, 11*. doi:10.3389/fonc.2021.646355
Xu, J., Bai, Y., Xu, N., Li, E., Wang, B., Wang, J., . . . Yuan, X. (2020). Tislelizumab Plus Chemotherapy as First-line Treatment for Advanced Esophageal Squamous Cell Carcinoma and Gastric/Gastroesophageal Junction Adenocarcinoma. *Clin Cancer Res, 26*(17), 4542-4550. doi:10.1158/1078-0432.Ccr-19-3561
Xu, X., Lai, Y., & Hua, Z.-C. (2019). Apoptosis and apoptotic body: disease message and therapeutic target potentials. *Bioscience reports, 39*(1), BSR20180992. doi:10.1042/BSR20180992
Xu, Y., Wang, Y., Gong, J., Zhang, X., Peng, Z., Sheng, X., . . . Shen, L. (2021). Phase I study of the recombinant humanized anti-HER2 monoclonal antibody-MMAE conjugate RC48-ADC in patients with HER2-positive advanced solid tumors. *Gastric Cancer, 24*(4), 913-925. doi:10.1007/s10120-021-01168-7
Yaghoobi, M., McNabb-Baltar, J., Bijarchi, R., & Hunt, R. H. (2017). What is the quantitative risk of gastric cancer in the first-degree relatives of patients? A meta-analysis. *World J Gastroenterol, 23*(13), 2435-2442. doi:10.3748/wjg.v23.i13.2435
Yamani, A., Zdżalik-Bielecka, D., Lipner, J., Stańczak, A., Piórkowska, N., Stańczak, P. S., . . . Wieczorek, M. (2021). Discovery and optimization of novel pyrazole-benzimidazole CPL304110, as a potent and selective inhibitor of fibroblast growth factor receptors FGFR (1-3). *Eur J Med Chem, 210*, 112990. doi:10.1016/j.ejmech.2020.112990
Yan, C., Bao, X., Shentu, W., Chen, J., Liu, C., Ye, Q., . . . Huang, P. (2016). Preoperative Gross Classification of Gastric Adenocarcinoma: Comparison of Double Contrast-Enhanced Ultrasound and Multi-Detector Row CT. *Ultrasound Med Biol, 42*(7), 1431-1440. doi:10.1016/j.ultrasmedbio.2016.01.030

Yan, T., Zhu, L., & Chen, J. (2023). Current advances and challenges in CAR T-Cell therapy for solid tumors: tumor-associated antigens and the tumor microenvironment. *Exp Hematol Oncol, 12*(1), 14. doi:10.1186/s40164-023-00373-7

Yang, P., Zhou, Y., Chen, B., Wan, H. W., Jia, G. Q., Bai, H. L., & Wu, X. T. (2009). Overweight, obesity and gastric cancer risk: results from a meta-analysis of cohort studies. *Eur J Cancer, 45*(16), 2867-2873. doi:10.1016/j.ejca.2009.04.019

Yashiro, M., & Matsuoka, T. (2016). Fibroblast growth factor receptor signaling as therapeutic targets in gastric cancer. *World J Gastroenterol, 22*(8), 2415-2423. doi:10.3748/wjg.v22.i8.2415

Yasuda, T., & Wang, Y. A. (2024). Gastric cancer immunosuppressive microenvironment heterogeneity: implications for therapy development. *Trends Cancer, 10*(7), 627-642. doi:10.1016/j.trecan.2024.03.008

Ychou, M., Boige, V., Pignon, J. P., Conroy, T., Bouché, O., Lebreton, G., . . . Rougier, P. (2011). Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. *J Clin Oncol, 29*(13), 1715-1721. doi:10.1200/jco.2010.33.0597

Ye, W., Chow, W.-H., Lagergren, J., Yin, L., & Nyrén, O. (2001). Risk of adenocarcinomas of the esophagus and gastric cardia in patients with gastroesophageal reflux diseases and after antireflux surgery. *Gastroenterology, 121*(6), 1286-1293. doi:https://doi.org/10.1053/gast.2001.29569

Yoon, S. H., Kim, K. Y., Wang, Z., Park, J. H., Bae, S. M., Kim, S. Y., . . . Jeon, J. Y. (2020). EW-7197, a Transforming Growth Factor-Beta Type I Receptor Kinase Inhibitor, Ameliorates Acquired Lymphedema in a Mouse Tail Model. *Lymphat Res Biol, 18*(5), 433-438. doi:10.1089/lrb.2018.0070

Yoshikawa, A. K., Yamaguchi, K., Muro, K., Takashima, A., Ichimura, T., Sakai, D., . . . Satoh, T. (2022). Safety and tolerability of andecaliximab as monotherapy and in combination with an anti-PD-1 antibody in Japanese patients with gastric or gastroesophageal junction adenocarcinoma: a phase 1b study. *J Immunother Cancer, 10*(1). doi:10.1136/jitc-2021-003518

Yoshikawa, K., & Maruyama, K. (1985). Characteristics of gastric cancer invading to the proper muscle layer--with special reference to mortality and cause of death. *Jpn J Clin Oncol, 15*(3), 499-503.

Yu, J., Fang, T., Yun, C., Liu, X., & Cai, X. (2022). Antibody-Drug Conjugates Targeting the Human Epidermal Growth Factor Receptor Family in Cancers. *Front Mol Biosci, 9*, 847835. doi:10.3389/fmolb.2022.847835

Zhang, C., Yu, G. M., Zhang, M., & Liu, D. (2020). S-1 plus apatinib as first-line palliative treatment for stage IVB gastroesophageal junction adenocarcinoma: A case report and review of the literature. *Medicine (Baltimore), 99*(1), e18691. doi:10.1097/md.0000000000018691

Zhang, F., Okazaki, U., Nakayama, I., & Shitara, K. (2026). CLDN18.2 in Gastric Cancer: Current Therapeutic Landscape and Future Perspectives. *J Gastric Cancer, 26*(1), 127-145. doi:10.5230/jgc.2026.26.e10

Zhang, H., Kong, Q., Wang, J., Jiang, Y., & Hua, H. (2020). Complex roles of cAMP–PKA–CREB signaling in cancer. *Experimental hematology & oncology, 9*(1), 32. doi:10.1186/s40164-020-00191-1

Zhang, J., Ji, D., Cai, L., Yao, H., Yan, M., Wang, X., . . . Hu, X. (2022). First-in-human HER2-targeted Bispecific Antibody KN026 for the Treatment of Patients with HER2-positive Metastatic Breast Cancer: Results from a Phase I Study. *Clin Cancer Res, 28*(4), 618-628. doi:10.1158/1078-0432.Ccr-21-2827

Zhang, Y., & Wang, X. (2020). Targeting the Wnt/β-catenin signaling pathway in cancer. *Journal of hematology & oncology, 13*(1), 165-165. doi:10.1186/s13045-020-00990-3

Zhao, Y., & Adjei, A. A. (2015). Targeting Angiogenesis in Cancer Therapy: Moving Beyond Vascular Endothelial Growth Factor. *Oncologist, 20*(6), 660-673. doi:10.1634/theoncologist.2014-0465

Zhen, L., Jiali, C., Yong, F., Han, X., Hongming, P., & Weidong, H. (2018). The Efficacy and Safety of Apatinib Treatment for Patients with Unresectable or Relapsed Liver Cancer: a retrospective study. *J Cancer, 9*(16), 2773-2777. doi:10.7150/jca.26376

Zheng, W., Sun, G., Li, Z., Wu, F., Sun, G., Cao, H., . . . Ma, Y. (2022). The Effect of Anlotinib Combined with anti-PD-1 in the Treatment of Gastric Cancer. *Front Surg, 9*, 895982. doi:10.3389/fsurg.2022.895982

Zhi, H., Xiang, Y., Chen, C., Zhang, W., Lin, J., Gao, Z., . . . Ma, C. (2024). Development and validation of a machine learning-based 18F-fluorodeoxyglucose PET/CT radiomics signature for predicting gastric cancer survival. *Cancer Imaging, 24*(1), 99. doi:10.1186/s40644-024-00741-4

Zhou, J., Sun, Y., Zhang, W., Yuan, J., Peng, Z., Wang, W., . . . Zhou, A. (2022). Phase Ib study of anlotinib combined with TQB2450 in pretreated advanced biliary tract cancer and biomarker analysis. *Hepatology*. doi:10.1002/hep.32548

Zhu, L., Zhu, C., Wang, X., Liu, H., Zhu, Y., & Sun, X. (2020). The Combination of Icotinib Hydrochloride and Fluzoparib Enhances the Radiosensitivity of Biliary Tract Cancer Cells. *Cancer Manag Res, 12*, 11833-11844. doi:10.2147/cmar.S265327

Zong, L., Abe, M., Seto, Y., & Ji, J. (2016). The challenge of screening for early gastric cancer in China. *The Lancet, 388*(10060), 2606. doi:https://doi.org/10.1016/S0140-6736(16)32226-7

ZW25 Effective in HER2-Positive Cancers. (2019). *Cancer Discovery, 9*(1), 8-8. doi:10.1158/2159-8290.Cd-nb2018-162

7 Appendix

7.1 Table of figures

7.2 Table of tables

7.3 Table of target genes

Drug	Gene Targets	Clinical Phases
(211-AT)OKT10-B10*	CD38	Phase I
[131I]-SGMIB Anti-HER2 VHH1*	ERBB2	Phase I&II
2X-121*	PARP1,PARP2,TNKS1,TNKS2	Phase II
9-ING-41*	GSK3A	Phase I&II
A166*	ERBB2	Phase II-IV
AB680*	NT5E	Phase I&II
ABBV-321*	EGFR	Phase I
ABBV-CLS-484*	PTPN2	Phase I
Abivertinib*	EGFR, BTK	Phase I-III
ABL503*	TNFRSF9	Phase I
ABM1310*	BRAF	Phase I
ABN401*	MET	Phase I/II
ABT-414*	EGFR	Phase I-III
ACE 1702*	ERBB2	Phase I
Adagrasib*	KRAS	Phase I&II
Adavosertib*	WEE1,CDK1,CDK2	Phase I&II
ADCT-602*	CD22	Phase I/II
Adebrelimab*	CD274	Phase I-III
ADG 106*	TNFRSF9	Phase I&II
AEE788*	EGFR,KDR,ERBB2	Phase I&II
AFM 24*	EGFR	Phase I/II
AFM13*	CD30	Phase I&II
afuresertib*	AKT1,AKT2,AKT3	Phase I&II
AG-270*	MAT2A	Phase I
AGEN2034*	PDCD1	Phase I-III
agerafenib*	EGFR	Phase I&II
AGS-16C3F*	ENPP3	discontinueddd
AK104*	PDCD1,CTLA4	Phase I-III
AK-109*	KDR	Phase I&II
AK112*	PDCD1,KDR,FLT1,FLT4	Phase I&II
AK117*	CD47	Phase I&II
AK119*	NT5E	Phase I
AL101*	NOTCH1,NOTCH2,NOTCH3,NOTCH4	Phase I-III
AL2846*	MET	Phase I&II
alflutinib mesylate*	EGFR	Phase I-III
Alisertib*	AURKA	Phase I-III
ALLO 501*	CD19	Phase I&II
ALLO 715*	TNFRSF17	Phase I
ALLO-316*	CD70	Phase I

Drug	Gene Targets	Clinical Phases
Almonertinib*	EGFR	Phase I-III
ALN-VSP*	KDR,FLT1,FLT4	Phase I
ALRN-6924*	MDM2	Phase I&II
Alsevalimab*	VTCN1	Phase I&II
ALT-P7*	ERBB2	Phase I
ALX 148*	CD47	Phase I-III
AMB-05X*	CSF1R	Phase II
AMC303*	CD44	Phase I
Amcenestrant*	ESR1	Phase I-III
AMG 160*	FOLH1	Phase I&II
AMG 232*	MDM2	Phase I-III
AMG 337*	MET	Phase I&II
AMG 404*	PDCD1	Phase I&II
AMG 420*	TNFRSF17	Phase I-III
AMG 562*	CD19	Phase I
AMG 595*	EGFR	Phase I
AMG 650*	KIF18A	Phase I
AMG 757*	DLL3	Phase I&II
AMG337*	MET	Phase I&II
AMG-650*	ESR1	Phase I
AMXI-5001*	PARP1,PARP2	Phase I/II
AN4005*	CD274	Phase I
anbenitamab*	ERBB2	Phase I&II
Andecaliximab*	MMP9	Phase I-III
Anetumab Ravtansine*	MSLN	Phase I&II
ANG1005*	LRP1	Phase III
AO-176*	CD47	Phase I/II
Apatinib *	KDR,FLT1,FLT4	Phase I-IV
APG 115*	MDM2	Phase I&II
APG 1387*	XIAP	Phase I&II
APG 2449*	ALK,PTK2,ROS1	Phase I
APG-115*	TP53,MDM2	Phase I&II
APG-2575*	BCL2	Phase I&II
APL-101*	MET	Phase I&II
APL-1202*	METAP2	Phase I-III
APN-431*	CBLB	no development reported
APTO 253*	MTF1	Phase I
APVO 436*	IL3RA	Phase I
APX 3330*	APEX1	Phase I&II
APX005M*	CD40	Phase I&II
Archexin*	AKT1	Phase I&II
ARO HIF2*	EPAS1	Phase I
ARQ 531*	BTK	Phase I&II
ARQ751*	AKT1,AKT2,AKT3	Phase I
ARRY 461*	CD47	Phase I
ARRY-382*	CSF1R	Phase I&II
ARV 110*	AR	Phase I/II
ARV-471*	ESR1	Phase I/II
ARX517*	FOLH1	Phase I
ARX788*	ERBB2	Phase I&II
asciminib*	DLL4,KDR	Phase I-III
ASN003*	BRAF,PTEN,PIK3CA	Phase I
ASP1650*	CLDN6	Phase II
ASTX029*	MAPK1,MAPK3	Phase I&II
ASTX295*	MDM2	Phase I/II
AT7519*	CDK1,CDK2,CDK4,CDK5,CDK6,CDK9	Phase I&II
Atamparib*	TIPARP	Phase I
ATG 019*	PAK4,NAMPT	Phase I
ATG-101*	CD274	Phase I
AV 203*	ERBB3	Phase I

Drug	Gene Targets	Clinical Phases
avitinib maleate*	EGFR	Phase I-III
axatilimab*	CSF1R	Phase I&II
AZD0466*	BCL2,BCL2L1	Phase I&II
AZD1390*	ATM	Phase I
AZD1480*	JAK2	Phase I
AZD4205*	JAK1	Phase I&II
AZD4547*	FGFR1,FGFR2,FGFR3	Phase I-III
AZD4573*	CDK9	Phase I
AZD4785*	KRAS	Phase I
AZD5153*	BRD4	Phase I&II
AZD-5305*	PARP1,PARP2	Phase I/II
AZD5991*	MCL1	Phase I
AZD8186*	PIK3CB	Phase I&II
AZD9496*	ESR1	Phase I
AZD9833*	ESR1	Phase I-III
BA 3011*	AXL	Phase I&II
balixafortide*	CXCR4	Phase I-III
barasertib*	AURKB	Phase I-III
Barecetamab*	ERBB3	Phase I
BAT 8001*	ERBB2	Phase I-III
Batiraxcept*	AXL	Phase I-III
BAY1143269*	EIF4E	Phase I
BAY1251152*	CDK9	Phase I
BAY1436032*	IDH1	Phase I
BAY1862864*	CD22	Phase I
BAY2315497*	FOLH1	Phase I
BAY2701438*	ERBB2	Phase I
BAY2701439*	ERBB2	Phase I
BAY2701439*	ERBB2	Phase I
BBP398*	PTPN11	Phase I
BBT-176*	EGFR	Phase I/II
BCA101*	EGFR,TGFB1	Phase I
BCD-115*	CDK8,CDK19	Phase I
BCD-147*	ERBB2	Phase I
BDC 1001*	ERBB2	Phase I/II
BDTX-189*	EGFR,ERBB2	Phase I/II
Belvarafenib*	BRAF,NRAS,KRAS,RAF1	Phase I&II
Bemarituzumab*	FGFR2	Phase I&II
Bemcentinib*	AXL	Phase I&II
Bermekimab*	IL1A	Phase I-III
Berzosertib*	ATR	Phase I&II
BGB-10188 *	PIK3CD	Phase I/II
BGB-16673*	BTK	Phase I
BGB3245*	BRAF	Phase I
BGB-3245*	BRAF	Phase I&II
BHQ-880 *	DKK1	Phase I&II
BI 1701963*	KRAS,SOS1	Phase I
BI 1810631*	ERBB2	Phase I
BI 1823911*	KRAS	Phase I
BI 3011441*	MAP2K1	Phase I
BI 754091*	PDCD1	Phase I&II
BI 836826*	CD37	Phase I&II
BI 836858*	CD33	Phase I&II
BI 853520*	PTK2	Phase I
BI 894999*	BET	Phase I
BI 905711*	CDH17	Phase I
BI 907828*	TP53,MDM2	Phase I
BI-754091*	PDCD1	Phase I&II
BIIB091*	BTK	Phase I
Bimiralisib*	PIK3CA,PIK3CB,PIK3CD,PIK3CG,MTOR	Phase I&II

Drug	Gene Targets	Clinical Phases
bintrafusp alfa*	PDCD1	Phase I-III
BION-1301*	TNFRSF13B,TNFRSF17	Phase I&II
Birabresib*	BRD2,BRD3,BRD4	Phase I&II
BJ 001*	ITGB3,ITGB5,ITGB6	Phase I
BL-8040*	CXCR4	Phase I-III
BLU-945*	EGFR	Phase I/II
BLZ945*	CSF1R	Phase I&II
BMS-599626*	EGFR,ERBB2,ERBB3,ERBB4	Phase I
BMS-690514*	EGFR,ERBB2,ERBB4,FLT1,FLT4,KDR	Phase I&II
BMS-813160*	CCR2,CCR5	Phase I&II
BMS-986004*	CD40	Phase I/II
BMS-986148*	MSLN	Phase I&II
BMS-986158*	BRD2,BRD3,BRD4,BRDT	Phase I&II
BMS-986179*	NT5E	Phase I/II
BOS172738*	RET	Phase I
Bozitinib*	MET	Phase I&II
BPI-1178*	CDK4,CDK6	Phase I/II
BPI15086*	EGFR	Phase I
BPI-15086*	EGFR	Phase I
BPI-9016M*	AXL,MET	Phase I
BPX-601*	PSCA	Phase I&II
BPX-701*	PRAME	Phase I/II
Briciclib*	CCND1	Phase I
Brilanestrant*	ESR1	Phase I
budigalimab*	PDCD1	Phase I&II
Buparlisib*	PIK3CA,PIK3CB,PIK3CD,PIK3CG	Phase I-III
burixafor*	CXCR4	Phase I&II
Burosumab*	FGF23	Phase I-III
BZ019*	CD19	Phase I
CA 4948*	IRAK4,FLT3	Phase I/II
CA-170*	CD274,PDCD1LG2,VSIR	Phase I&II
CA-4948*	IRAK4	Phase I/II
cabiralizumab*	CSF1R	Phase I&II
Camidanlumab tesirine*	IL2RA	Phase I&II
Camrelizumab*	PDCD1	Phase I-III
CAN008*	FAS	Phase I&II
capivasertib*	AKT1,AKT2,AKT3	Phase I&II
carotuximab*	ENG	Phase I-III
Catequentinib*	FGFR1,FGFR2,FGFR3,FGFR4,KIT,PDGFRA,PDGFRB,RET,KDR,FLT4	Phase I-IV
Catumaxomab*	EPCAM	Phase I-III
CB-010*	CD19	Phase I&II
CB-03-10*	NR3C1,AR	Phase I
CB-103*	NOTCH1,NOTCH2,NOTCH3,NOTCH4	Phase I/II
CB307*	FOLH1	Phase I
CC 90010*	BRD2,BRD3,BRD4,BRDT	Phase I&II
CC 97540*	CD19	Phase I
CC 98633*	TNFRSF17	Phase I
CC-90002*	CD47	Phase I
CC-90003*	MAPK1	Phase I
CC-90011*	KDM1A	Phase I&II
CC-98633*	TNFRSF17	Phase I
CCS1477*	EP300	Phase I/II
CCT303-406*	ERBB2	Phase I
CDX-1140*	CD40	Phase I&II
CDX-301*	FLT3	Phase I&II
CDX-3379*	ERBB3	Phase I&II
CDX-527*	CD274	Phase I
Cediranib*	KDR,FLT1,FLT4	Phase I-III
CEP-11981*	TEK,KDR,FLT1,FLT4	Phase I&II
Ceralasertib*	ATR	Phase I&II

Drug	Gene Targets	Clinical Phases
Cerdulatinib*	SYK,JAK1,JAK3	Phase I-III
Cergutuzumab amunaleukin*	CEACAM5	Phase I
cetrelimab*	PDCD1	Phase I-III
CFI 402257*	TTK	Phase I&II
CFI-400945*	PLK4	Phase I&II
CFI-402257*	TTK	Phase I&II
CG-806*	FLT3,BTK	Phase I
CHC2014*	NTRK1,NTRK2,NTRK3	Phase I
Chiauranib*	KIT,KDR,PDGFR,AURKB,FLT1,FLT4	Phase I-III
CHO-H01*	MS4A1	Phase I
cibisatamab*	CEACAM5	Phase I&II
CID-103*	CD38	Phase I
cinrebafusp alfa*	ERBB2	Phase I
Cirmtuzumab*	ROR1	Phase I&II
Cirtuvivint*	WNT1	Phase I
CKD-702*	EGFR,MET	Phase I
CLIC-1901*	CD19	Phase I/II
CLN-081*	EGFR	Phase I/II
CM313*	CD38	Phase I
CM93*	EGFR,EGFRVIII	Phase I
CMB305*	CTAG1B	Phase I&II
Cofetuzumab pelidotin*	PTK7	Phase I
Cosibelimab*	PDCD1	Phase I-III
COTI 2*	TP53,AKT1,AKT2,AKT3	Phase I
CPGJ602*	EGFR	Phase I&II
CPI-006*	NT5E	Phase I-III
CPI-1205*	EZH2	Phase I&II
CPI-818*	ITK	Phase I
CPL304110*	FGFR1,FGFR2,FGFR3,FGFR4	Phase I
CPO107*	MS4A1,CD47	Phase I/II
crenigacestat*	NOTCH1,NOTCH2,NOTCH2,NOTCH4	Phase I&II
Crenolanib*	PDGFRA,PDGFRB,FLT3	Phase I-III
CT 0508*	ERBB2	Phase I-IV
CT041*	CLDN18	Phase I&II
CT053*	TNFRSF17	Phase I&II
CT7001*	CDK7	Phase I/II
CTT1057*	FOLH1	Phase I-III
CTT1403*	FOLH1	Phase I
CTX 130*	CD70	Phase I-IV
CX-2009*	ALCAM	Phase I&II
CYH33*	PIK3CA	Phase I&II
CYT-0851*	RAD51	Phase I/II
D-0316*	EGFR	Phase I-III
D-0502*	ESR1	Phase I
D-1553*	KRAS	Phase I/II
Dactolisib*	PIK3CA,PIK3CD,PIK3CG,MTOR	Phase I-III
Dalpiciclib*	CDK4,CDK6	Phase I-III
Danusertib*	AURKB,AURKA,AURKC	Phase II
Danvatirsen*	STAT3	Phase I&II
Darovasertib*	PRKCA,PRKCQ,GSK3B	Phase I&II
datopotamab deruxtecan*	TACSTD2	Phase I-III
DBPR112*	EGFR	Phase I
DCC-3116*	ULK1,ULK2	Phase I
DCLL9718S*	CLEC12A	Phase I
DCR-MYC*	MYC	Phase I
Defactinib*	PTK2	Phase I&II
Depatuxizumab*	EGFR	Phase I-III
derazantinib*	FGFR1,FGFR2,FGFR3	Phase I&II
DF1001*	PDCD1	Phase I/II
DFF332*	EPAS1	Phase I

Drug	Gene Targets	Clinical Phases
DHES0815A*	ERBB2	Phase I
Disitamab vedotin*	ERBB2	Phase I-III
Divozilimab*	MS4A1	Phase I&II
DKN-01*	DKK1	Phase I&II
domatinostat*	HDAC1,HDAC2,HDAC3,BRD4	Phase I&II
dovitinib*	KIT,PDGFRA,FLT3,KDR,FGFR3,FLT1,FLT4	Phase I-III
DP303c*	ERBB2	Phase I
DS 1055a*	LRRC32	Phase I
DS-1001*	IDH1	Phase I&II
DSP107*	CD47	Phase I&II
DSP-7888*	WT1	Phase I-III
DT2216*	BCL2L1	Phase I
DT2219ARL*	CD19,CD22	Phase I&II
DTRM-555*	MTOR,BTK	Phase I&II
Dubermatinib*	AXL	Phase I&II
DZD9008*	EGFR	Phase I&II
E 6201*	MAP2K1,MAP3K1	Phase I&II
E7090*	FGFR1,FGFR2,FGFR3	Phase I&II
EC 0652*	FOLH1	Phase I
EC1169*	FOLH1	Phase I
Eganelisib*	PIK3CG	Phase I&II
Elimusertib*	ATR	Phase I
Elranatamab*	TNFRSF17	Phase I-III
eltanexor*	XPO1	Phase I/II
EMB-01*	MET,EGFR	Phase I-III
Enoblituzumab*	CD276	Phase I-III
Ensartinib*	ALK	Phase I-III
Entospletinib*	SYK	Phase I-III
Envafolimab*	PDCD1	Phase I-III
enzastaurin*	PIK3CA,PRKCB,AKT1,AKT2,AKT3	Phase I-III
EP-100 *	GNRH1	Phase I&II
Epacadostat*	IDO1	Phase I-III
epitinib*	EGFR	Phase I
Epratuzumab*	CD22	Phase I-III
Eprenetapopt*	p53	Phase I-III
ERAS-007*	MAPK3,MAPK1	Phase I/II
ERY974*	GPC3	Phase I
ESG401*	TACSTD2	Phase I&II
ETH-155008*	FLT3,CDK4,CDK6	Phase I
Fadraciclib*	CDK2,CDK9,CDK5	Phase I&II
Famitinib*	KIT,PDGFR,FLT4,FLT3,KDR	Phase I-III
Farletuzumab*	FOLR1	Phase I&II
FAZ053*	CD274	Phase I
FCN-011*	NTRK1,NTRK2,NTRK3	Phase I
FCN159*	MAP2K1,MAP3K1	Phase I&II
FCN411*	EGFR,ERBB2	Phase I/II
FCN-437*	CDK4,CDK6	Phase I&II
Felezonexor*	XPO1	Phase I
FF-10101-01*	FLT3	Phase I/II
FHD-286*	SMARCA4, SMARCA2	Phase I
FHD-609*	BRD9	Phase I
Fibromun*	FN1	Phase I&II
Ficlatuzumab*	MET	Phase I&II
Fimepinostat*	PIK3CA,PIK3CB,PIK3CD,HDAC1	Phase I&II
Fisogatinib*	FGFR4,FGF19	Phase I&II
Flotetuzumab*	IL3RA	Phase I&II
Flumatinib*	PDGFR,KIT	Phase I-IV
Fluzoparib*	PARP1,PARP2	Phase I-III
FOR46*	CD46	Phase I-IV
Foritinib succinate*	ALK,ROS1	Phase I/II

Drug	Gene Targets	Clinical Phases
FPX 01*	IGF1R	Phase I
fruquintinib*	KDR,FLT1,FLT4	Phase I-IV
FS118*	CD274	Phase I/II
FS-1502*	ERBB2	Phase I
FS222*	PDCD1	Phase I
FT 596*	CD19	Phase I
FT 7051*	CREBBP,EP300,AR	Phase I
FT-1101*	BRD2,BRD3,BRD4,BRDT	Phase I
Futibatinib*	FGFR1,FGFR2,FGFR3,FGFR4	Phase I-III
Futuximab/modotuximab - Symphogen*	EGFR	Phase I-III
G1T48*	ESR1	Phase I
Galunisertib*	TGFBR1	Phase I-III
GC022F *	CD19,CD22	Phase I&II
GC1118*	EGFR	Phase I&II
GDC-0919*	IDO1	Phase I
GDC-0927*	ESR1	Phase I
GDC-6036*	KRAS	Phase I
Gedatolisib*	PIK3CA,PIK3CD,PIK3CG,PIK3CB,MTOR	Phase I&II
GEM333*	CD33	Phase I
GEM-3-PSCA*	PSCA	Phase I
GEN1044*	TPBG	Phase I&II
GEN1046*	PDCD1	Phase I&II
genolimzumab*	PDCD1	Phase I&II
Giredestrant*	ESR1	Phase I-III
glembatumumab vedotin*	GPNMB	Phase I&II
glofitamab*	MS4A1	Phase I-III
Glumetinib*	MET	Phase I&II
GNR-084*	CD19	Phase I/II
GQ 1001*	ERBB2	Phase I
GS-3583*	FLT3	Phase I
GSK2141795*	AKT1,AKT2,AKT3	Phase I&II
GSK2256098*	PTK2	Phase I&II
GSK2636771*	PIK3CB	Phase I&II
GSK2636771*	PIK3CB	Phase I&II
GSK2849330*	ERBB3	Phase I
GSK3145095*	RIPK1	Phase II
GSK3368715*	PRMT1	Phase I
GST-HG161*	MET	Phase I
GT90001*	ALK1	Phase I/II
Gusacitinib*	JAK1,JAK2,JAK3,TYK2,SYK	Phase I&II
H3B-6527*	FGFR4	Phase I
H3B-6545*	ESR1	Phase I&II
HB0025*	CD274	Phase I
HEC 68498*	MTOR,PIK3CA,PIK3CB,PIK3CG,PIK3CD	Phase I
HH2710*	MAPK3,MAPK1	Phase I/II
HL-085*	MAP3K1,RAF1	Phase I&II
HLX 208*	BRAF	Phase I&II
HLX20*	CD274	Phase I
HLX22*	ERBB2	Phase I&II
HLX23*	NT5E	Phase I
HLX55*	MET	Phase I
HM95573*	BRAF,RAF1	Phase I
HMPL306*	IDH1,IDH2	Phase I
HMPL-453*	FGFR1,FGFR2,FGFR3	Phase I&II
HMPL-523*	SYK	Phase I-III
HPN328*	DLL3	Phase I/II
HPN536*	MSLN	Phase I/II
HS 10241*	MET	Phase I&II
HS-10342*	CDK4,CDK6	Phase I&II
HS-10352*	PIK3CA	Phase I

Drug	Gene Targets	Clinical Phases
HS269*	RET	Phase I
HWH340*	PARP1,PARP2	Phase I
HX008*	PDCD1	Phase I-III
I-131-Apamistamab*	PTPRC	Phase I
IAH0968*	ERBB2	Phase I/II
Ianalumab*	TNFSF13B	Phase I-III
IBI315*	PDCD1,ERBB2	Phase I
IBI318*	CD274	Phase I&II
IBI322*	CD274	Phase I
IBI323*	CD274	Phase I
Icotinib*	EGFR	Phase I-IV
ICP-192*	FGFR1,FGFR2,FGFR3,FGFR4	Phase I&II
Idasanutlin*	MDM2	Phase I-III
IDE397*	MAT2A	Phase I
IDH305*	IDH1	Phase I&II
Idronoxil*	ENOX2	Phase I-III
IDX-1197*	PARP1,PARP2	Phase I&II
Ifabotuzumab*	EPHA3	Phase I&II
IGM 2323*	MS4A1	Phase I
IGM-8444 *	TNFRSF10B	Phase I
Ilorasertib*	PDGFRA,PDGFRB,PDGFC,PDGFD,KDR,AURKA,AURKB,AURKC,FLT1,FLT4	Phase I&II
Imalumab*	MIF	Phase I&II
Imaradenant*	ADORA2A	Phase I&II
IMC CS4*	CSFR1	Phase I
IMC001*	CD274	Phase I&II
IMC002*	CD47	Phase I
IMC-3C5*	FLT4	Phase I
IMGN632*	IL3RA	Phase I/II
IMGN779*	CD33	Phase I
IMM0306*	MS4A1,CD47	Phase I
IMP4297*	PARP1,PARP2	Phase I-III
IMP7068*	WEE1	Phase I
IMP-7068*		
Inavolisib*	PIK3CA,PIK3CB,PIK3CD,PIK3CG	Phase I-III
INBRX-105*	TNFRSF9,PDCD1	Phase I&II
INCB057643*	BRD2,BRD3,BRD4,BRDT	Phase I&II
INCB059872*	KDM1A	Phase I&II
INCB062079*	FGFR4	Phase I
INCB086550*	CD274	Phase I&II
INCB099280*	CD274	Phase I
INCB099318*	PDCD1	Phase I
INCB7839*	ADAM10,ADAM17	Phase I&II
Indatuximab ravtansine*	SDC1	Phase I&II
INO5401*	WT1,FOLH1,TERT	Phase I&II
Ipatasertib*	AKT1	Phase I-III
IRX4204*	RXRA	Phase I&II
ISB 1342*	CD38	Phase I
Itacitinib*	JAK1	Phase I-III
JAB-21822*	KRAS G12C	Phase I/II
JAB-3068*	PTPN11	Phase I&II
JAB-3312*	KRAS	Phase I&II
JDQ443*	KRAS G12C	Phase I/II
JMT101*	EGFR	Phase I
JNJ-40346527*	CSF1R	Phase I&II
JNJ-67571244*	CD33	Phase I
JNJ-67856633*	MALT1	Phase I
JNJ-74699157*	KRAS	Phase I
JNJ-75229414*	KLK2	Phase I
JNJ-75276617*	KMT2A	Phase I
JNJ-75348780*	CD22	Phase I

Drug	Gene Targets	Clinical Phases
JNJ-78278343*	KLK2	Phase I
JPI-547*	PARP1,PARP2,TNKS1,TNKS2	Phase I
JSI-1187*	MAP2K1,MAP2K2	Phase I
KA2237*	PIK3CB,PIK3CD	Phase I
KA2507*	HDAC6	Phase I&II
Kanitinib*	MET,KDR	Phase I
KB-0742*	CDK9	Phase I
KD 033*	PDCD1	Phase I
KHK 2823*	IL3RA	Phase I
KIN-2787*	BRAF	Phase I
KITE-222*	CLEC12A	Phase I&II
KITE-585*	TNFRSF17	Phase I&II
KN046*	CD274,CTLA4	Phase I-III
KO-539*	KMT2A	Phase I&II
KPT-9274*	NAMPT,PAK4	Phase I
larotinib*	EGFR,ERBB2,ERBB3,ERBB4	Phase I-III
Lazertinib*	EGFR	Phase I-III
L-DOS 47*	CEACAM6	Phase I&II
Lenzilumab*	CSF2	Phase I-III
Lerociclib*	CDK4,CDK6	Phase I&II
letetresgene autoleuce*	CTAG1B	Phase I&II
Lifirafenib*	EGFR,BRAF	Phase I&II
Linperlisib*	PIK3CD	Phase I&II
lintuzumab*	CD33	Phase I-III
LM-061*	MET	Phase I&II
LM-302*	CLDN18	Phase I/II
LMB-100*	MSLN	Phase I&II
Lodapolimab*	PDCD1	Phase I
Loncastuximab tesirine*	CD19	Phase I-III
Lorvotuzumab mertansine*	NCAM1	Phase I&II
LOXO-305*	BTK	Phase I-III
LP002*	CD274	Phase I&II
LTT462*	MAPK1	Phase I&II
Lucitanib*	FGFR1,FGFR2,FGFR3,FGFR4,PDGFRA,PDGFRB,KIT,RAF1,KDR,FLT1,FLT4	Phase I-III
Lumretuzumab*	ERBB3	Phase I&II
Lutetium-177 rosapatamab*	FOLH1	Phase I-III
LVGN7409*	CD40	Phase I
LXI-15029*	MTOR	Phase I
LY011*	CLDN18	Phase I
LY2874455*	FGFR1,FGFR2,FGFR3,FGFR4	Phase I
LY3022855*	CSF1R	Phase I&II
LY3076226*	FGFR3	Phase I
LY3200882*	TGFBR1	Phase I&II
LY3214996*	MAP3K1,MAPK1	Phase I&II
LY3295668*	AURKA	Phase I&II
LY3300054*	CD274	Phase I
LY3321367*	HAVCR2	Phase I
LY3410738*	IDH1	Phase I
LY3434172*	CD274	Phase I
LY3475070*	NT5E	Phase I
LY3484356*	ESR1	Phase I-III
LY3499446*	KRAS	Phase I/II
LY3537982*	KRAS G12C	Phase I
LYT-200*	LGALS9	Phase I/II
M1774*	ATR	Phase I
M4344*	ATR	Phase I&II
M802*	ERBB2	Phase I
Magrolimab*	CD47	Phase I-III
Masitinib*	KIT,PDGFR,FGFR3,FYN,CSF1R,LYN,PTK2	Phase II&III
Mavelertinib*	EGFR	Phase I/II

Drug	Gene Targets	Clinical Phases
MAX-40279*	FGFR1,FGFR2,FGFR3,FLT3	Phase I&II
MB 101*	CD19	Phase I-III
MB 102*	IL3RA	Phase I-III
MB 103*	ERBB2	Phase I-III
MB 104*	SLAMF7	Phase I-IV
MCLA 145*	PDCD1	Phase I
MCLA-129*	EGFR,MET	Phase I&II
MCLA-145*	CD274	Phase I
MCS110*	CSF1R	Phase I&II
MCY M11*	MSLN	Phase I
MDG1011*	PRAME	Phase I/II
MEDI4276*	ERBB2	Phase I
MEN 1112*	BST1	Phase I
MEN1611*	PIK3CA	Phase I&II
Merestinib*	MST1R,MET,FLT3,AXL,MERTK,TEK,ROS1,DDR1,DDR2,MKNK1,MKNK2	Phase I&II
Metatinib *	BCR,ABL1	Phase I
Mezagitamab*	CD38	Phase I&II
MGCD265*	TEK,MET,MST1R,KDR,CSF1R,AXL,FLT1,FLT4	Phase I&II
MGD 007*	GPA33	Phase I&II
Mipetresgene autoleucel*	CTAG1B	Phase I
Miransertib*	AKT1,AKT2,AKT3	Phase I&II
mirdametinib*	MAPK1	Phase I&II
mirvetuximab*	FOLR1	Phase I-III
mitazalimab*	CD40	Phase I&II
Mivavotinib*	FLT3,SYK	Phase I&II
MK 2206*	AKT1,AKT2,AKT3	Phase I&II
MK2206*	AKT1,AKT2,AKT3	Phase I-III
MK-4830*	LILRB2	Phase I&II
MK-7684A*	PDCD1	Phase I-III
MM-302*	ERBB2	Phase I
Mobocertinib*	EGFR,ERBB2	Phase I&II
molibresib besylate*	BRD2,BRD3,BRD4,BRDT	Phase I&II
Momelotinib*	JAK1,JAK2	Phase I-III
Monalizumab*	KLRC1	Phase I-III
MOR202*	CD38	Phase I&II
mosunetuzumab*	MS4A1	Phase I-III
MP 0250*	KDR,HGF,FLT1,FLT4	Phase I/II
MP 0310*	FAP	Phase I
MP0274*	ERBB2	Phase I
MRG002*	ERBB2	Phase I&II
MRG003*	EGFR	Phase I&II
MRX-2843*	FLT3,MERTK	Phase I&II
MSB2311 *	CD274	Phase I
MT 5111*	ERBB2	Phase I&II
MT-3724*	MS4A1	Phase I&II
MTL-CEBPA*	CEBPA	Phase I&II
Naporafenib*	BRAF,RAF1	Phase I&II
Naptumomab estafenatox*	TPBG	Phase I-III
Naquotinib*	EGFR	Phase I-III
Naratuximab emtansine*	CD37	Phase I&II
Navicixizumab*	DLL4,KDR,FLT1,FLT4	Phase I
Nazartinib*	EGFR	Phase I-III
Nemiralisib*	PIK3CD	Phase I-III
NG-641 *	FAP	Phase I
NGM707*	LILRB1, LILRB2	Phase I/II
Nimotuzumab*	EGFR	Phase I-IV
ningetinib tosylate*	MET,KDR,AXL,MERTK,FLT3	Phase I/II
NIS793*	TGFB1	Phase I-III
NJH395*	ERBB2	Phase I
NKX-101 *	KLRK1	Phase I

Drug	Gene Targets	Clinical Phases
NMS-03305293*	PARP1	Phase I&II
NMS-03592088*	CSF1R,KIT,FLT3	Phase I/II
NP-137 *	NTN1	Phase I&II
NT 219*	STAT3	Phase I/II
NTX-301*	DNMT1	Phase I&II
NX-2127*	BTK	Phase I
NZV930*	NT5E	Phase I
Obrindatamab*	CD276	Phase II
OBT076*	LY75	Phase I
Odronextamab*	MS4A1	Phase I&II
OKT10-B10*	CD38	Phase I
Olafertinib*	EGFR	Phase I/II
oleclumab*	NT5E	Phase I&II
olinvacimab*	KDR	Phase I&II
olmutinib*	EGFR	Phase I&II
olutasidenib*	IDH1	Phase I&II
Olverembatinib*	FLT3,KIT	Phase I&II
OMO 1*	MET	Phase I/II
OMP-305B83*	DLL4,KDR,FLT1,FLT4	Phase I
Onalespib*	HSP90AA1,HSP90AB1	Phase I&II
Onapristone*	ESR1	Phase I&II
onatasertib*	MTOR	Phase I&II
ONC 201*	AKT1,AKT2,AKT3,MAPK1	Phase I&II
ONC 206*	DRD2	Phase I
ONO-7579*	NTRK1,NTRK2,NTRK3	Phase I
ONO-7701*	IDO1	Phase I&II
Ontorpacept*	CD47	Phase I&II
Onvansertib*	PLK1	Phase I-III
opaganib*	SPHK2	Phase I-III
Oportuzumab*	EPCAM	Phase I-III
orelabrutinib*	BTK	Phase I-IV
Orvacabtagene autoleucel*	TNFRSF17	Phase II
OS 2966*	ITGB1	Phase I
OTS 167*	MELK	Phase I&II
Paclitaxel trevatide*	LRP1	Phase I-III
Pacmilimab*	PDCD1	Phase I&II
Pacritinib*	FLT3,JAK2	Phase I-III
Pamiparib*	PARP1,PARP2	Phase I-III
Pamufetinib*	MET,KDR,FLT1,FLT4	Phase I&II
Parsaclisib*	PIK3CD	Phase I-III
Patidegib*	SMO	Phase I-III
patritumab*	ERBB3	Phase I-III
Paxalisib*	PIK3CA,PIK3CB,PIK3CD,PIK3CG	Phase I-III
PBI-200*	NTRK1,NTRK2,NTRK3	Phase I/II
PC14586*	p53	Phase I/II
pelabresib*	BRD2,BRD3,BRD4,BRDT	Phase I-III
pelcitoclax*	BCL2L1,BCL2	Phase I&II
Pemrametostat*	PRMT5	Phase I&II
PEN 221*	SSTR2	Phase I/II
PEN 866*	HSP90AA1,HSP90AB1	Phase I&II
Penpulimab*	PDCD1	Phase II/III
Petosemtamab*	EGFR,LGR5	Phase I
pexmetinib*	MAPK11,MAPK12,MAPK13,MAPK14,TEK,SRC,KDR	Phase I&II
PF-03084014*	NOTCH1,NOTCH2,NOTCH3,NOTCH4	Phase I-III
PF-06459988*	EGFR	Phase II
PF-06671008*	CDH3	Phase I
PF-06688992*	ST8SIA1	Phase I
PF-06804103*	ERBB2	Phase I
PF-06873600*	CDK2,CDK4,CDK6	Phase I&II
PF-07104091*	CDK2	Phase II

Drug	Gene Targets	Clinical Phases
PF-07209960*	PDCD1	Phase I
PF-07248144*	KAT6A,KAT6B	Phase I
PF-07257876*	CD47	Phase I
PF-07284892*	PTPN11	Phase I
PF-114*	BCR,ABL1	Phase I/II
PHI-101*	CHEK2	Phase I
Pictilisib*	PIK3CA,PIK3CD	Phase I&II
Pidilizumab*	PDCD1	Phase I-IV
Pimasertib*	MAP2K1, MAP2K2	Phase I&II
Pimitespib*	HSP90AA1,HSP90AB1	Phase I
pimivalimab*	CD274	Phase I
pirotinib*	ERBB2,EGFR,EPHB4	Phase I&II
Plamotamab*	MS4A1	Phase I
PLX2853*	BRD4	Phase I
PLX51107*	BRD1,BRD2,BRD3,BRD4	Phase I&II
PLX8394*	BRAF,RAF1	Phase I&II
PLX9486*	KIT	Phase I&II
PMD-026*	RPS6KA2,RPS6KA1,RPS6KA3,RPS6KA6	Phase I
Poziotinib*	EGFR,ERBB2	Phase I&II
Praluzatamab ravtansine*	ALCAM	Phase I&II
Prexasertib*	CHEK1	Phase I&II
PRGN-3005 *	MUC16	Phase I
PRI-724*	CTNNB1,CREB1,WNT1	Phase I&II
PRL3-ZUMAB*	PTP4A3	Phase I&II
PRN1371*	FGFR1,FGFR2,FGFR3,FGFR4,CSFR1	Phase I
PRT 543*	PRMT5	Phase I
PRT1419*	MCL1	Phase I
PSB202*	MS4A1	Phase I
PT2385*	EPAS1	Phase I&II
PTC596*	BMI1	Phase I
Pyrotinib*	EGFR,ERBB2	Phase I-III
Q 702*	AXL,MERTK,TNFRSF17	Phase I-III
Q-1802*	CD274,CLDN18	Phase I
QBS10072S*	SLC7A4	Phase I
QL-1209*	ERBB2	Phase I
QLS31901*	CD274	Phase I
Quizartinib*	FLT3	Phase I-III
Radotinib *	PDGFR,SNCAIP	Phase I-III
Ralimetinib*	MAPK1	Phase I&II
RC108*	MET	Phase I&II
RC48-ADC*	ERBB2	Phase I-III
refametinib*	MAP2K1	Phase I&II
REGN 4018*	MUC16	Phase I/II
REGN 5458*	TNFRSF17	Phase I/II
REGN 5668*	MUC16	Phase I/II
REGN5093*	MET	Phase I/II
REGN7075*	EGFR	Phase I&II
Relatlimab*	LAG3	Phase I-III
Repotrectinib *	NTRK1,NTRK2,NTRK3,ALK,SRC,ROS1,PTK2	Phase I&II
retifanlimab*	PDCD1	Phase I-III
Rezivertinib*	EGFR	Phase I-III
RGX-202-01 *	SLC6A8	Phase I
ricolinostat*	HDAC6	Phase I&II
Rigosertib*	BCR,ABL1,PLK1,PLK2,PDGFR,SRC,FYN,FLT1	Phase I-III
RLY-1971*	PTPN11	Phase I
RLY-4008*	FGFR2	Phase I
RMC4630*	PTPN11	Phase I&II
RMC-4630*	PTPN11	Phase I&II
RMC-5552*	MTOR	Phase I
RO 7122290*	FAP	Phase I/II

Drug	Gene Targets	Clinical Phases
RO 7172508*	CECAM5	Phase I
RO 7227166*	CD19	Phase I
RO5126766*	MAP2K1	Phase I&II
RO6870810*	BRD2,BRD3,BRD4,BRDT	Phase I
RO6958688*	CECAM5	Phase I&II
RO7051790*	KDM1A	Phase I
RO7122290*	FAP	Phase I/II
RO7227166*	CD19	Phase I
RO7247669*	PDCD1	Phase I&II
RO7284755*	PDCD1	Phase I
RO7293583*	TYRP1	Phase I
Rociletinib*	EGFR	Phase I-III
Rogaratinib*	FGFR1,FGFR2,FGFR3,FGFR4	Phase I-III
roniciclib*	CDK1,CDK2,CDK4,CDK9	Phase I&II
RP12146*	PARP1,PARP2	Phase I
RP-3500*	ATR	Phase I/II
runimotamab*	ERBB2	Phase I
RVU120*	CDK8,CDK19	Phase I&II
RX 5902*	BCL2,CDKN1A	Phase I/II
RXC004*	PORCN	Phase I&II
RXC-004 *	WNT1	Phase I&II
sabatolimab*	HAVCR2	Phase I-III
Samotolisib*	PIK3CA,PIK3CB,PIK3CD,PIK3CG,MTOR	Phase I&II
Samuraciclib*	CDK7	Phase I/II
Sapanisertib*	CTRC	Phase I&II
Sapitinib*	EGFR	Phase I&II
SAR 442257*	CD38	Phase I
SAR125844*	MET	Phase I&II
SAR428926*	LAMP1	Phase I
SAR439459*	TGFB1	Phase I&II
SAR443216*	ERBB2	Phase I
Saracatinib*	SRC,ABL1	Phase I-III
Sasanlimab*	PDCD1	Phase I-III
Savolitinib*	MET	Phase I-III
SBT6050*	ERBB2,EGFR	Phase I
SC10914*	PARP1,PARP2	Phase I&II
SCT200*	EGFR	Phase I&II
seclidemstat*	KDM1A	Phase I/II
Selitrectinib*	NTRK1,NTRK2,NTRK3	Phase I&II
Serabelisib*	PIK3CA	Phase I&II
Seribantumab*	ERBB3	Phase I&II
serplulimab*	PDCD1	Phase I-III
Sevacizumab*	KDR,FLT1,FLT4	Phase I
SF1126*	PIK3CA,PIK3CB,PIK3CD,PIK3CG,MTOR	Phase I&II
SG301*	CD38	Phase I
SGT-53*	TP53	Phase I&II
SH-1028 *	EGFR	Phase I-III
SH3809*	PTPN11	Phase I
SHR1701*	CD274	Phase I-III
SHR2554*	EZH2	Phase I&II
Shr3680*	AR	Phase I-III
SHR7390*	MAP2K1	Phase I&II
SHR-A1811*	ERBB2	Phase I&II
SI-B001*	EGFR,ERBB3	Phase I-III
Silmitasertib*	CSNK2A1	Phase I&II
SIM1803-1A*	NTRK1,NTRK2,NTRK3,ROS1,ALK	Phase I
Simlukafusp alfa*	FAP	Phase I&II
Simurosertib*	CDC7	Phase I&II
Sintilimab*	PDCD1	Phase I-III
Siremadlin*	MDM2	Phase I&II

Drug	Gene Targets	Clinical Phases
Sitravatinib*	EPHB1,AXL,MET,MERTK,MST1R,KDR,FLT1,FLT4	Phase I-III
SKB-264 *	TACSTD2	Phase I/II
SKLB1028*	EGFr,FLT3,ABL1	Phase I-III
SLC-391*	AXL	Phase I
SNDX-5613*	KMT2A	Phase I/II
SNX-5422 *	HSP90AA1,HSP90AB1	Phase I&II
Socazolimab*	PDCD1	Phase I-III
SOR-C13*	TRPV6	Phase I
Spartalizumab*	CD274	Phase I-III
Spebrutinib*	BTK	Phase I&II
SRA737*	CHEK1	Phase I/II
SRF 617*	ENTPD1	Phase I
SRF617*	ENTPD1	Phase I
Stenoparib*	PARP1,PARP2,TNKS	Phase I&II
STI-1492*	CD38	Phase I
STI-6129*	CD38	Phase I
Surufatinib*	KDR,FGFR1,CSF1R,FLT1,FLT4	Phase I-III
SX682*	CXCR1,CXCR2	Phase I&II
SX-682*	CXCR1,CXCR2	Phase I&II
SXL01*	AR	Phase I
SY-1365*	CDK7	Phase I
SY-5609*	CDK7	Phase I
SYHA1801*	BRD4	Phase I
Sym015*	MET	Phase I/II
SYN004*	EGFR	Phase I&II
SYN125*	PDCD1	Phase I
T-1101*	PCSK2	Phase I
TAC01-CD19*	CD19	Phase I/II
TAK 007*	CD19	Phase II
TAK 169*	CD38	Phase I
TAK 573*	CD38	Phase I&II
TAK-164*	GUCY2C	Phase I
TAK-580*	ARAF,BRAF,RAF1	Phase I&II
Talacotuzumab*	IL3RA	Phase I-III
taletrectinib*	NTRK1,NTRK2,NTRK3,ROS1	Phase II
TAS0612*	AKT1,AKT2,AKT3,RPS6KA1,RPS6KB1,YBX1	Phase I
TAS0728*	ERBB2	Phase I/II
TAS0953/HM06*	RET	Phase I/II
TAS-117*	AKT1,AKT2,AKT3	Phase II
TAS2940*	ERBB2,EGFR	Phase I
taselisib*	PIK3CA	Phase I-III
Tebentafusp*	PMEL	Phase I&II
telisotuzumab vedotin*	MET	Phase I-III
Telomelysin*	TERT	Phase I&II
tenalisib*	PIK3CD,PIK3CG	Phase I&II
Tepoditamab*	CLEC12A	Phase I
Tesevatinib*	ERBB2,EGFR,EPHB4	Phase I&II
TG-1801*	CD47,CD19	Phase I
Tipifarnib*	CXCL12	Phase I-III
Tirabrutinib*	BTK	Phase I&II
Tislelizumab*	PDCD1	Phase I-III
tivantinib*	MET	Phase I-III
TK 216*	FLI1,ETS1	Phase I&II
TL-895*	BTK	Phase I&II
TNB-383B*	TNFRSF17	Phase I
TNB-486*	CD19	Phase I
TNB-585*	FOLH1	Phase I
TNO155*	PTPN11	Phase I&II
Tolinapant*	XIAP,BIRC2	Phase I&II
tomivosertib*	MKNK1,MKNK2,PDCD1	Phase I&II

Drug	Gene Targets	Clinical Phases
Toripalimab*	CD274	Phase I-III
TP 1287*	CDK9	Phase I
TP-0184*	ACRV1	Phase I&II
TPX-0022*	MET,SRC,CSFR1	Phase I
TPX0046*	SRC,RET	Phase I/II
TPX-0046*	RET,SRC	Phase I/II
TQ-B211*	ERBB2	Phase III
TQB2450*	CD274	Phase II
TQ-B3101*	ALK,ROS1,MET	Phase I&II
TQ-B3139*	ALK,MET	Phase I-III
TQB3303*	CDK4,CDK6	Phase I
TQB3455*	IDH2	Phase I
TQB3525*	PIK3CA,PIK3CD	Phase I/II
TQ-B3525*	PIK3CA,PIK3CD	Phase I&II
TQB3616*	CDK4,CDK6	Phase I&II
TQB3823*	PARP1,PARP2	Phase I
TQB3909*	BCL2	Phase I
TR1801-ADC*	MET	Phase I
Trabedersen*	TGFBR2	Phase I-III
TRC253*	AR	Phase I/II
Tremelimumab*	CTLA4	Phase I-III
Triciribine phosphate*	AKT1,AKT2,AKT3	Phase I&II
TRPH-222*	CD22	Phase I
TT-00420*	AURKA,AURKB	Phase I&II
TTI-101*	STAT3	Phase I
TTI-621*	CD47	Phase I&II
TTI-622*	CD47	Phase I
TTX 030*	ENTPD1	Phase I
Tucidinostat*	HDAC1,HDAC2,HDAC3,HDAC10,AKT1,AKT2,AKT3,MAP3K1,PIK3CA	Phase I-IV
TVB-2640*	FASN	Phase I&II
TY-9591*	EGFR	Phase I
Ublituximab*	MS4A1	Phase I-III
Uliledlimab*	NT5E	Phase I&II
Ulixertinib*	MAPK3,MAPK1	Phase I&II
Ulocuplumab*	CXCR4	Phase I&II
Unesbulin*	BMI1	Phase I
Vactosertib*	TGFBR1	Phase I&II
Varlilumab*	CD27	Phase I&II
Varlitinib*	EGFR,ERBB2	Phase I-III
VC004*	NTRK1,NTRK2,NTRK3	Phase I/II
Veliparib*	PARP1,PARP2	Phase I-IV
VG161*	PDCD1	Phase I
Vibecotamab*	IL3RA	Phase I
vimseltinib*	CSF1R	Phase I-III
VIP152*	CDK9	Phase I
vistusertib*	MTOR	Phase I&II
VLS-101*	ROR1	Phase I&II
VLX1570*	UCHL5,USP14	Phase I
VMD-928*	NTRK1	Phase I
Vofatamab*	FGFR3	Phase I-IV
vorasidenib*	IDH1,IDH2	Phase I&III
Vorolanib*	PDGFRA,PDGFRB,KDR,FLT1,FLT4	Phase I-III
VS 6766*	MAP2K1,RAF1	Phase I&II
VT30*	PIK3CA	Phase I/II
VT3989*	TEAD1,TEAD2,TEAD3,TEAD4	Phase I
vudalimab*	PDCD1	Phase I&II
Vulinacimab*	KDR	Phase I
W0101*	IGF1R	Phase I
WP1066*	JAK2	Phase I
WSD0922-FU*	EGFR,EGFR	Phase I

Drug	Gene Targets	Clinical Phases
Xevinapant*	BIRC2,BIRC3,XIAP	Phase I-III
XL 092*	MET,KDR,FLT1,FLT4	Phase I
XL888*	HSP90AA1,HSP90AB1	Phase I
XmAb18087*	SSTR2	Phase I&II
XMT-1522*	ERBB2	Phase I
XY0206*	FLT3	Phase I
XZP-3287*	CDK4,CDK6	Phase I-III
XZP-5809-TT1*	EGFR	Phase I
XZP-5955*	ROS1,NTRK1,NTRK2,NTRK3	Phase I/II
YS 110*	DPP4	Phase I/II
YYB101*	MET	Phase I&II
Zanidatamab*	ERBB2,SEM1	Phase I&II
ZB716*	ESR1	Phase I/II
ZEN003694*	BRD2,BRD3,BRD4,BRDT	Phase I&II
Zenocutuzumab*	ERBB2,ERBB3	Phase I&II
Zimberelimab*	PDCD1	Phase I-III
ZN-A-1041*	ERBB2	Phase I
ZN-c3*	WEE1	Phase I&II
ZN-e4*	EGFR	Phase I/II
Zolbetuximab*	CLDN18	Phase I-III
Zorifertinib*	EGFR	Phase I-III
Zotatifin*	EIF4A1	Phase I&II
Zotiraciclib*	CDK1,CDK2,CDK7,CDK9,JAK2,FLT3	Phase I&II
ZW 49*	ERBB2	Phase I
ZX-101A*	PIK3CD,PIK3CG	Phase I/II
ZZ06*	EGFR	Phase I

8 Publication of results

Chiapponi, C., **Hartmann, M. J. M.,** Decarolis, B., Simon, T., Bruns, C. J., Faust, M., Schultheis, A. M., Schmidt, M., & Alakus, H. (2023). Differentiated Thyroid Cancer in Adolescents: Single Center Experience and Considerations for Surgical Management and Radioiodine Treatment. *Journal of clinical research in pediatric endocrinology*. Advance online publication. https://doi.org/10.4274/jcrpe.galenos.2023.2023-1-16

Chiapponi, C., **Hartmann, M. J. M.,** Schmidt, M., Faust, M., Bruns, C. J., Schultheis, A. M., & Alakus, H. (2022). Hürthle Cell Carcinoma: Single Center Analysis and Considerations for Surgical Management Based on the Recent Literature. *Frontiers in endocrinology*, *13*, 904986. https://doi.org/10.3389/fendo.2022.904986

Hescheler, D. A., **Hartmann, M. J. M.,** Riemann, B., Michel, M., Bruns, C. J., Alakus, H., & Chiapponi, C. (2022). Targeted Therapy for Adrenocortical Carcinoma: A Genomic-Based Search for Available and Emerging Options. *Cancers,* 14(11), 2721. https://doi.org/10.3390/cancers14112721

Chiapponi, C., Santos, D. P. D., **Hartmann, M. J. M.,** Schmidt, M., Faust, M., Wahba, R., Bruns, C. J., Schultheis, A. M., & Alakus, H. (2022). Adrenal Surgery in the Era of Multidisciplinary Endocrine Tumor Boards. *Hormone and metabolic research = Hormon- und Stoffwechselforschung = Hormones et metabolisme*, *54*(5), 294–299. https://doi.org/10.1055/a-1808-7239

Hescheler, D. A., **Hartmann, M. J. M.**, Riemann, B., Michel, M., Bruns, C. J., Alakus, H., & Chiapponi, C. (2022). Anaplastic thyroid cancer: genome-based search for new targeted therapy options. *Endocrine connections*, *11*(4), e210624. https://doi.org/10.1530/EC-21-0624

Chiapponi, C., **Hartmann, M. J. M.,** Schmidt, M., Faust, M., Schultheis, A. M., Bruns, C. J., & Alakus, H. (2021). Radioiodine Refractory Follicular Thyroid Cancer and Surgery for Cervical Relapse. *Cancers*, *13*(24), 6230. https://doi.org/10.3390/cancers13246230

Hescheler, D. A., Riemann, B., **Hartmann, M. J. M.,** Michel, M., Faust, M., Bruns, C. J., Alakus, H., & Chiapponi, C. (2021). Targeted Therapy of Papillary Thyroid Cancer: A Comprehensive Genomic Analysis. *Frontiers in endocrinology*, *12*, 748941. https://doi.org/10.3389/fendo.2021.748941