Hubertus Wald Tumorzentrum
Universitäres Cancer Center Hamburg
Ein Kompetenznetzwerk des UKE

Investigational Plan & Clinical Study Protocol

Ipilimumab or FOLFOX in combination with Nivolumab and Trastuzumab in previously untreated HER2 positive locally advanced or metastatic EsophagoGastric Adenocarcinoma

The randomized phase 2 INTEGA trial.

Sponsor: AIO-Studien-gGmbH

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Investigator's Agreement

I have read the attached protocol entitled

"Ipilimumab or FOLFOX in combination with Nivolumab and Trastuzumab previously untreated HER2 positive locally advanced or metastatic EsophagoGastric Adenocarcinoma."

Version FINAL 4.0, 31-Jan-2018

and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice (ICH-GCP).

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the study sponsor.

Signature

Investigator

Date (DD Month YYYY)

Investigator's Institution

Study Glossary

Abbreviation/Acronym	Definition
ADL	Activities of daily living
ADR	Adverse Drug Reaction
AE	Adverse event
AIDS	Acquired Immune Deficiency Syndrome
AMG	Arzneimittelgesetz
ANC	Absolute neutrophil count
aPTT	Activated Partial Thromboplastin Time
ALT (SGPT)	Alanine aminotransferase (serum glutamic-pyruvic transaminase)
AST (SGOT)	Aspartate aminotransferase (serum glutamic-oxaloacetic transaminase)
BMS	Bristol-Myers Squibb
BSA	Body surface area
CA 19-9	Carbohydrate antigen 19-9
CD	Cluster of Differentiation
CEA	Carcinoembryonic antigen
CI	Confidential Interval
eCRF	Electronic Case Report Form
CMO	Contract Manufacturing Organization
CNS	Central Nervous System
CrP	C reactive Protein
CT	Computerized tomography
CTC	Circulating Tumor cells
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating Tumor DNA
CTLA4	Cytotoxic T-Lymphocyte-Associated protein 4
CTx	Chemotherapy
CVA	Cerebrovascular accident
EBV	Epstein Barr Virus
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGA	Esophagogastric adenocarcinoma
eGFR	Estimated Glomerular Filtration Rate
EORTC	European Organization of Research and Treatment of Cancer
FDA	Food and Drug Administration (U.S. government agency)
FFPE	Formalin-Fixed Paraffin-Embedded

FOLFOX	FOLinic acid 5-Fluorouracil OXaliplatin
FSH	Follicle Stimulating Hormone
FU	5-Flurouracil
GC	Gastric Carcinoma
GCP	Good Clinical Practice
GCP-V	Verordnung über die Anwendung der Guten Klinischen Praxis (GCP) bei der Durchführung von klinischen Prüfungen mit Arzneimitteln zur Anwendung am Menschen
GEJ	GastroEsophagel Junction
HBsAg	Hepatitis-B virus surface Antigen
HCV	Hepatitis-C Virus
HER	Human epidermal growth factor receptor
HIV	Human Immundeficiency Virus
HR	Hazard Ratio
HT	HydroxyTryptamin
ICF	Informed consent form
IDMC	Independent Data Monitoring Committee
IEC	Independent ethics committee
IGH	Immunoglobulin heavy locus
IHC	ImmunHistoChemistry
IMP	Investigational medicinal product
INR	International normalized ratio
IRB	Institutional Review Board
ISH	In-Situ Hybridization
ITT	Intention-to-treat
IU	International Unit
IV	intravenous
LDH	Lactate hydrogenase
LFT	Liver Function Test
LV	Leucovorin
LVEF	left ventricular ejection fraction
LVSD	left ventricular systolic dysfunction
MUGA	MUltiGated Aquisition
MDRD	Modification of Diet in Renal Disease
MRI	Magnetic resonance imaging
MSI	Microsatellite Instability
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NGS	Next generation sequencing
NYHA	New York Heart Association

ORR	Overall Response Rate
OS	Overall survival
mOS	median Overall Survival
PD	Progressive Disease
PD-L1	Programmed Death Receptor Ligand 1
PEI	Paul Ehrlich Institut
PFS	Progression Free Survival
PIK3CA	PhosphatIdylinositol-4,5-bisphosphate 3-kinase, Catalytic subunit Alpha
PTT	Partial thromboplastin time
QoL	Quality of life
RBC	Red blood cell count
RDE	Remote data entry
RECIST	Response Evaluation Criteria in Solid Tumors
RR	Response Rate
SADR	Serious adverse drug reaction
SAE	Serious adverse event
SAR	Seriour adverse reaction
SAS	Statistic software
SDV	Source Data Verification
SEER	Surveillance, Epidemiology, and End Results Program
SLD	Sum of the longest diameters
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TCRß	T-cell receptor beta
TIL	Tumor-infiltrating lymphocytes
TNM	Classification of malignant tumors
TSH	Thyroid-Stimulating Hormone
ULN	Upper limit of normal
WBC	White blood cell count
WOBCP	Women of Child Bearing Potential

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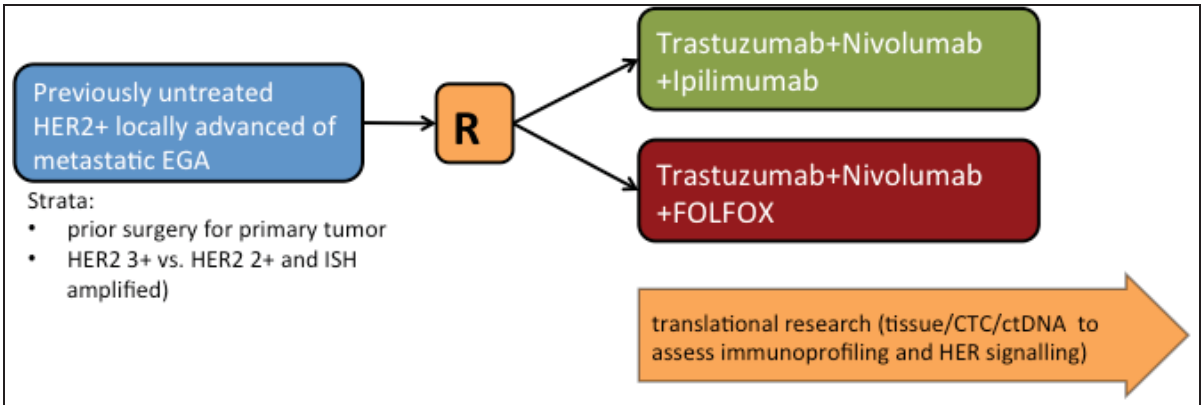
Synopsis

Title	Ipilimumab or FOLFOX in combination with Nivolumab and Trastuzumab in previously untreated HER2 positive locally advanced or metastatic EsophagoGastric Adenocarcinoma The randomized phase 2 INTEGA trial.
Design	Randomized, open labelled, multicenter phase II trial
Indication	Patients with previously untreated metastatic HER2 positive esophagogastric adenocarcinoma
Sample Size	97 patients to be included
Study Duration	Duration of recruitment: 24 months at a rate of 4 patients/month (counted from at least 50% of sites activated). Follow-up from last patient in to primary endpoint or end of safety follow up 3 months after last administration of up to 12 months of nivolumab +/- ipilimumab (up to 15 months). Further follow-up for survival until trial termination 48 months after first patient in. Expected total trial duration 4 years.
Endpoints	Primary endpoint: • Overall Survival including milestone rate @ 12 months Secondary endpoints: • Safety and tolerability (acc. to NCI CTC AE v4.03 and to the obtained data on vital signs, clinical parameters and feasibility of the regimen) • Progression Free Survival (PFS) according to RECIST v1.1 • Response Rate (RR) according to RECIST v1.1 • Quality of life (EORTC QLQ-C30 and STO-22) • Translational research (correlation of immune response signatures, changes in HER2 and PD-L1 and HER signaling status in tissue, CTC and ctDNA with efficacy • central imaging review and determination of ORR and PFS according to modified RECIST)
Trial Overview	



Inclusion Criteria	1. All subjects must have inoperable, advanced or metastatic GC or GEJ carcinoma and have histologically confirmed predominant adenocarcinoma. The documentation of GEJ involvement can include biopsy, endoscopy, or imaging. 2. Subjects must have HER2-positive disease defined as either IHC 3+ or IHC 2+, the latter in combination with ISH+, as assessed locally on a primary or metastatic tumour (*Note:* Availability of formalin-fixed paraffin-embedded (FFPE) representative tumor tissue for central confirmation of HER2 is mandatory (Preferably fresh biopsy)) 3. Subject must be previously untreated with systemic treatment (including HER 2 inhibitors) given as primary therapy for advanced or metastatic disease. 4. Prior adjuvant or neoadjuvant chemotherapy, radiotherapy and/or chemoradiotherapy are permitted as long as the last administration of the last regimen (whichever was given last) occurred at least 6 months prior to randomization. 5. Subjects must have measurable or evaluable non-measurable disease as assessed by the investigator, according to RECIST v1.1 (Appendix D). 6. ECOG performance status score of 0 or 1 (Appendix B). 7. Screening laboratory values must meet the following criteria (using NCI CTCAE v.4.03): a. WBC ≥ 2000/uL b. Neutrophils ≥ 1500/µL c. Platelets ≥ $100x10^3$/µL d. Hemoglobin ≥ 9.0 g/dL e. eGFR ≥ 30ml/min f. AST ≤ 3.0 x ULN (or ≤ 5.0X ULN if liver metastates are present) g. ALT ≤ 3.0 x ULN (or ≤ 5.0X ULN if liver metastates are present)

	h. Total Bilirubin ≤ 1.5 x ULN (except subjects with Gilbert Syndrome who must have a total bilirubin level of < 3.0 x ULN) 8. Males and Females, ≥ 18 years of age 9. Subjects must have signed and dated an IRB/IEC approved written informed consent form in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol-related procedures that are not part of normal subject care. 10. Subjects must be willing and able to comply with scheduled visits, treatment schedule, laboratory tests and other requirements of the study. 11. Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study drug. Women must not be breastfeeding. 12. WOCBP must use a highly effective method(s) of contraception for a period of 30 days (duration of ovulatory cycle) plus the time required for the investigational drug to undergo 5 half-lives. The terminal half-lives of nivolumab and ipilimumab are approximately 25 days and 15 days, respectively. WOCBP should use an adequate method to avoid pregnancy for approximately 5 months (30 days plus the time required for nivolumab to undergo 5 half-lives) after the last dose of investigational drug. 13. Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for a period of 90 days (duration of sperm turnover) plus the time required for the investigational drug to undergo 5 half-lives. The terminal half-lives of nivolumab and ipilimumab are approximately 25 days and 15 days, respectively. Males who are sexually active with WOCBP must continue contraception for approximately 7 months (90 days plus the time required for nivolumab to undergo 5 half-lives) after the last dose of investigational drug. In addition, male subjects must be willing to refrain from sperm donation during this time.
Exclusion Criteria	1. Malignancies other than disease under study within 5 years prior to inclusion, with the exception of those with a negligible risk of metastasis or death (e.g., expected 5-year OS > 90%) treated with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, localized prostate cancer treated surgically with curative intent, ductal carcinoma in situ treated surgically with curative intent) 2. Subjects with untreated known CNS metastases. Subjects are eligible if CNS metastases are adequately treated and subjects are neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment) for at least 2 weeks prior to randomization. In addition, subjects must be either off corticosteroids, or on a stable or decreasing dose of < 10 mg

	daily prednisone (or equivalent) for at least 2 weeks prior to randomization. 3. History of exposure to the following cumulative doses of anthracyclines (epirubicin > 720 mg/m^2, doxorubicin or liposomal doxorubicin > 360 mg/m^2, mitoxantrone > 120 mg/m^2 and idarubicin > 90 mg/m^2, other (other anthracycline greater than the equivalent of 360 mg/m^2 of doxorubicin). If more than one anthracycline has been used, then the cumulative dose must not exceed the equivalent of 360 mg/m^2 of doxorubicin 4. Baseline LVEF value < 55%, assessed by echocardiogram, multigated acquisition (MUGA) scan, or cardiac magnetic resonance imaging (MRI) scan 5. Subjects with active, known, or suspected autoimmune disease. Subjects with Type I diabetes mellitus, residual hypothyroidism due to autoimmune thyroiditis only requiring hormone replacement, or skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment are permitted to enroll. For any cases of uncertainty, it is recommended that the medical monitor be consulted prior to signing informed consent. 6. Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids, and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease. 7. Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways. 8. Persisting toxicity related to prior therapy (NCI CTCAE v. 4.03 Grade > 1); however, alopecia, sensory neuropathy Grade ≤ 2, or other Grade ≤ 2 not constituting a safety risk based on investigator's judgment are acceptable. 9. Any serious or uncontrolled medical disorder or active infection that, in the opinion of the investigator, may increase the risk associated with study participation, study drug administration, or would impair the ability of the subject to receive study drug. 10. Significant acute or chronic infections including, among others: a. Any positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS) b. Any positive test result for hepatitis B virus or hepatitis C virus indicating acute or chronic infection. 11. History of allergy or hypersensitivity to study drugs or any constituent of the products 12. History of allogeneic tissue/solid organ transplant 13. Participation in another clinical study with an investigational product during the last 30 days before inclusion

	14. Patient who has been incarcerated or involuntarily institutionalized by court order or by the authorities § 40 Abs. 1 S. 3 Nr. 4 AMG. 15. Patients who are unable to consent because they do not understand the nature, significance and implications of the clinical trial and therefore cannot form a rational intention in the light of the facts [§ 40 Abs. 1 S. 3 Nr. 3a AMG].
Treatment, Dosage and Administration	All eligible patients will be randomized, stratified for prior surgery of primary tumour and HER2 postivity status to **Arm A** **Week 1-12** Trastuzumab 6mg/kg d1 every 3 weeks (loading dose 8mg/kg) Nivolumab 1mg/kg i.v. d1 every 3 weeks Ipilimumab 3mg/kg i.v. d1 every 3 weeks **Week 13 till EOT** Trastuzumab 4mg/kg d1 every 2 weeks Nivolumab 240mg i.v. d1 every 2 weeks **Arm B** Trastuzumab 4mg/kg d1 every 2 weeks (loading dose 6mg/kg) Nivolumab 240mg i.v. d1 every 2 weeks mFOLFOX6 every 2 weeks Oxaliplatin at a dose of 85 mg/m^2 IV over two hours (day 1) 5-FU 400 mg/m^2 IV bolus (day 1) LV at a dose of 400 mg/m^2 iv over two hours (day 1) 5-FU at a dose of 2400 mg/m^2 IV over 46 hours (day 1-3) **Duration of treatment** Treatment with trastuzumab, nivolumab and ipilimumab or FOLFOX will be administered until progression (according to RECIST v1.1), intolerable toxicity, withdrawal of consent or secondary resection. The treatment with nivolumab will be limited to a maximum of 12 months (24 applications of nivolumab). Ipilimumab will only be applied in weeks 1, 4, 7, and 10.
Assessments	**Baseline (within 4 weeks before treatment start)** • Review of inclusion and exclusion criteria • Medical and medication history, physical examination including height, weight, vital signs (blood pressure, heart rate, respiratory rate, body temperature), oxygen saturation, ECOG-performance status • Laboratory Tests: o Hematology panel: hemoglobin, red blood cell (RBC) count, platelets, white blood cell (WBC) count and WBC differential (neutrophils, lymphocytes) o Chemistry panel: sodium, potassium, calcium, magnesium, creatinine, urea, total bilirubin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate

	aminotransferase (AST), total protein, albumin, LDH, glucose, amylase, lipase o Free T3/T4 and TSH o Coagulation: INR, aPTT o CA 72-4 (CEA, CA 19-9 optional) o Hepatitis B/C screening test (HBsAg, anti-HBc, anti-HBs, anti-HCV) o HIV screening test (HIV 1/2 antigen/antibody test) o Pregnancy test for women of childbearing potential within 24 hours prior to start of the treatment • Blood draw for translational research • Obtain paraffin-embedded tumor-tissue for translational research • Echocardiography and ECG • Quality of life assessment (EORTC QLQ-C30 and STO-22) • Disease assessment by radiological imaging of the chest, abdomen, pelvis and all other sites of disease (CT/MRI-scan) **During treatment (at start of treatment and every 2 or 3 weeks, +3/-2 days previous to any new cycle) (**safety-relevant assessments, including pregnancy test have to be completed before dosing) • Physical examination including oxygen saturation, performance status (ECOG), assessment of toxicity, concomitant medication • Laboratory tests (hematology and chemistry panel), including • Free T3/T4 and TSH (every 6 weeks) • Pregnancy test for women of childbearing potential (every 4 weeks) • Quality of life assessment (EORTC QLQ-C30 and STO-22) every 2 months (together with imaging) • Blood draw for translational research (cycle 2,5 and progression and/or end of treatment) • Echocardiography every 3 months **Additional assessments during treatment with nivolumab, ipilimumab and trastuzumab in arm A until week 13 on day 12 of every cycle (+/-3 days)** • Physical examination including oxygen saturation, performance status (ECOG), assessment of toxicity, concomitant medication • Laboratory tests (hematology and chemistry panel) **Final staging** When any subject discontinues dosing of all study treatment, the following assessments should be made: • Physical examination including oxygen saturation, performance status (ECOG), assessment of toxicity, concomitant medication • Laboratory tests (baseline panel), including free T4 and TSH and pregnancy test for women of childbearing potential

	• Echocardiography and ECG • Disease assessment by radiological imaging of the chest, abdomen, pelvis and all other sites of disease (CT/MRI-scan) **30 and 100 days safety follow-up (±7 days)** • Physical examination including oxygen saturation, performance status (ECOG), assessment of toxicity, concomitant medication • Laboratory tests (hematology and chemistry panel), including free T3/T4 and TSH and pregnancy test for women of childbearing potential **Extended safety follow-up** Given the potential risk for delayed immune-related toxicities, safety follow-up must be performed every 30 days up to 100 days after the last dose of nivolumab+/- ipilimumab. The extended safety follow-up beyond 30 days after last study drug administration may be performed either via a site visit or via a telephone call with subsequent site visit requested in case any concerns noted during the telephone call. **Follow-up** All subjects will be followed every 3 months ± 28 days for up to 4 years after start of recruitment. In case of progressive disease after study treatment only: • Survival, disease status, protracted toxicity, further treatment In any other case additionally: • Disease assessment, physical examination including weight, ECOG-performance status • Blood draw for translational research at progression **Tumor Response Assessment** During treatment tumor response will be assessed every 8 weeks (±7 days) for up to 12 months and afterwards 3 monthly by the investigator according to RECIST v1.1 (Radiological imaging by CT and/or MRI of the chest, abdomen, pelvis and all other sites of disease). After treatment discontinuation for other than progressive disease imaging will be performed according to standard of care until progression or death. CT and/or MRI scans will be independently reviewed, thus blinded data will be collected. **Safety** Safety assessments will include physical examinations with vital signs (blood pressure, heart rate, respiratory rate, ioxygen saturation and body temperature), performance status (ECOG), clinical laboratory profile and adverse events. All observed toxicities and side effects will be graded according to NCI CTCAE v4.03 for all patients and the degree of association of each with the procedure assessed and summarized. Treatment related serious adverse events rate (SAE) will be determined.

	Quality of Life Quality of life will be assessed using the EORTC QLQ-C30 and STO-22 every 8 weeks together with tumor response assessment.
Translational Research	The following translational research is currently planned, but may be adapted taking into account new research data • Tumor-infiltrating lymphocytes (TiL) repertoire determination from tumor • Liquid biopsy next-generation sequencing (NGS) immunoprofiling (*TCRβ* & *IgH*) before treatment initiation and before second cycle to determine response predictive immune signature (diversification pattern as read-out for ongoing immune activation, TiL clone expansion in peripheral blood) • In addition FFPE will be centrally tested for PD-L1, HER2 (IHC and ISH), MSI, EBV and HER signaling alterations (amplifications and/or mutations in e.g. EGFR, HER2, HER3, PIK3CA) and correlated with clinical efficacy. • CTC will be evaluated for changes in HER2 and PD-L1 status • ctDNA will be evaluated for HER signaling alterations (amplifications and/or mutations in e.g. EGFR, HER2, HER3, PIK3CA) • Central imaging review and determination of ORR and PFS according to modified RECIST (refer to appendix D). Thus, the tumor block for TiL analysis, HER2, PD-L1 and HER signaling assessment will be obtained at baseline. Blood will be collected prior to first treatment and beginning of cycle 2 and 5 and at progression and/or end of treatment. In addition, imaging will be retrospectively collected.
Statistical Considerations	The present trial is designed as a randomized phase II study, which aims to estimate the therapeutic efficacy of two experimental regimen. OS analysed according to the ITT principle is the primary efficacy endpoint. The efficacy assumptions are derived from historical data. The TOGA trial has defined the standard 1st line treatment with chemotherapy and trastuzumab with a 12-month-OS rate (OSR@12) of 55% (median OS of 13.8 months) (Bang, Van Cutsem et al. 2010). Nivolumab in chemotherapy refractory patients (median 3 prior treatment lines) results in an overall response rate of 11-14% and a median OS of about 5.3 months (Janjigian, Bendell et al. 2016, Kang, Satoh et al. 2017). The combination of nivolumab and ipilimumab in the same patient population results in an overall response rate of 26% and a median OS of about 6.9 months (Janjigian, Bendell et al. 2016). The INTEGA trial will evaluate two experimental regimen in 1st line HER2 positive EGA treatment, a chemo-free regimen with trastuzumab+nivolumab+ipilimumab and a intensified TOGA-like regimen with trastuzumab+nivolumab+FOLFOX. Each of the experimental arms would be considered promising, if the true 12-month-OS rate amounts to 70 %. This translates into a hazard ratio of 0.6 compared to the standard OSR@12 of 55% for chemotherapy and trastuzumab.

	Sample size estimation: Based on these assumptions, and an exponential shape of the survival curves, a one-sided logrank test with a sample size of 41 subjects achieves 80% power at a one-sided significance level of 0.05 to detect a hazard ratio of 0.6 when the proportion surviving with the current standard is 0.55 (OSR@12 months). Overall 82 patients will be included and randomized into the two experimental arms (41 in each experimental treatment group). The rate of drop-outs is estimated to be 15%. Hence, the total number of subjects to be recruited is N= 97. This calculation assumes an accrual time of 24 months, and a minimum follow-up of 15 months of all patients alive at the time point of analysis. Randomization will be performed according to the following stratification criteria: • Prior surgery of the primary tumour yes vs. no • HER2 status IHC 3+ vs. IHC 2+ and ISH amplified
Early Toxicity Analysis	Based on the novel combination regimen applied in this study the IDMC will monitor safety and efficacy data every 3 to 6 months throughout the trial. In addition a safety run-in phase will be conducted to detect potential safety risks early. **Safety Run-In Phase for the first 15 patients** After at least two months of treatment of the 5th, 10th and 15th patient per arm the IDMC will review the safety data respectively and decide about trial continuation. Regular IDMC Meetings will be performed every 3 months until the last patient has passed the 2 months assessments and afterwards every 6 months to review safety data until the last administration of nivolumab.

Flow chart (figure 1)

Study Schedule Visit	Inclusion	During treatment		End of Treatment	Safety follow up	Follow up
Study week (wks)	Baseline (within 4 wks prior to cycle 1)	Cycle 1, day1 afterwards every 2/3 wks (+3/-2 d)	Day 12 (+/-3 d) until wk 13 only in arm A		After 30 and 100 d [7] (±7 d)	every 3 months (±28 d)
Informed consent	X					
Eligibility criteria	X					
Medical history, demographics	X					
Physical examination[1]	X	X	X	X	X	X[6]
Vital signs[2]	X	X	X	X		
Oxygen saturation	X	X	X	X	X	
Performance status (ECOG)	X	X	X	X	X	X
Echocardiography and ECG	X	X[8]		X		
Obtain tumor tissue	X					
Blood draw translat. research	X	X[4]		X		X[10]
Laboratory determinations[3]	X	X	X	X	X	
Treatment		X				
Tumor markers (CA 72-4, optional CEA, CA 19-9)	X	X[5]		X		X[6]
Quality of life assessment (EORTC QLQ C30 and STO 22)	X	X[5]		X		(x)[5]
Tumor assessment (CT/MRI)	X	X[5]		X		X[6]
Concomitant medication	X	X		X	X	
Further treatment						X
AE monitoring/ assessment of toxicity	X					X[9]
Survival	X					

1: including heart, chest, abdomen, skin, lymph nodes, neurological exam, inspection of accessible mucosa and weight, height (only baseline)
2: blood pressure, heart rate, respiratory rate, body temperature
3: hematology panel (hemoglobin, platelets, WBC with neutrophils, lymphocytes), chemistry panel (sodium, potassium, calcium, magnesium, serum creatinine, urea, alkaline phosphatase, AST, ALT, total bilirubin, glucose, lipase, amylase) screening at baseline, day 1 prior every treatment cycle, (in arm A until week 13 on day 12 of every cycle), EOT and 30 days safety follow up; coagulation (INR, aPTT), LDH, albumine, and total protein, screening at baseline and EOT; HIV, hepatitis b/c screening only baseline; serum pregnancy test in women of childbearing potential screening at baseline and every 4 weeks, EOT and 30 days safety follow up and free T3/T4 and TSH at baseline, every 6 weeks, EOT and 30 days safety follow up
4: blood draw baseline and cycle 2 and 5 and end of treatment
5: during treatment every 8 weeks (±7 days) for 12 months afterwards every 3 months, after treatment discontinuation for other than progressive disease imaging will be performed according to standard of care until progression or death..
6: only in case of no progressive disease during or after 1st line treatment
7: safety follow up should be on site
8: echocardiography every 3 months
9. protracted toxicity
10. at progression (if not reason for EOT)

1. Introduction and Background

1.1 Epidemiology and Disease Background

Gastric cancer is the fifth most common cancer in the world, with an estimated 951,000 new cases diagnosed in 2012 (6.8% of total cancer cases), and the third leading cause of cancer death in both sexes worldwide, with 723,000 deaths (8.8% of total cancer deaths) estimated in that year (Ferlay, Soerjomataram et al. 2015). In Europe, 139,600 new cases were diagnosed and 107,300 patients died of gastric cancer in 2012 (Ferlay, Steliarova-Foucher et al. 2013). Gastric cancer is more frequent among males and ist incidence increases with age, peaking between 65 and 74 years of age (Ferlay, Soerjomataram et al. 2015). The incidence of tumors located in the gastric cardia and gastroesophageal junction has increased in past decades and is linked to risk factors such as obesity and gastroesophageal reflux disease (Buas and Vaughan 2013).

Surgical resection is currently the only curative treatment option for gastric cancer; however, ~50% of patients have metastatic disease at the time of diagnosis and chemotherapy is the mainstay of palliation in this setting (Smyth, Verheij et al. 2016). Best supportive care (BSC) plus chemotherapy has been shown to be more effective than BSC alone in patients with advanced gastric cancer, with combination chemotherapy more effective than single-agent treatment (Wagner, Unverzagt et al. 2010).

Current treatment options in first line patients with unresectable or metastatic esophagogastric adenocarcinoma are candidates for chemotherapy-based palliative treatment only; with a doublet of a platinum compound and a fluoropyrimidine currently regarded as an acceptable standard first-line option (Smyth, Verheij et al. 2016)

The use of targeted treatments in the first-line therapy of advanced gastric cancer is also evolving and paving the way for personalized medicine [17], although human epidermal receptor type 2 (HER2) status is currently the only validated molecular marker to influence decision-making in advanced disease [3]. Trastuzumab, in combination with capecitabine and cisplatin or 5-FU and cisplatin, significantly improved survival in patients with overexpression of HER2 (Bang, Van Cutsem et al. 2010), but only 20% of gastric cancers and 30% of gastroesophageal cancers overexpress HER2 (Maresch, Schoppmann et al. 2011).

1.2 Checkpoint Inhibition in Esophagogastric Adenocarcinoma

Nivolumab (BMS-936558), a programmed cell death protein-1 (PD-1) antibody, with or without ipilimumab (BMS-734016), a cytotoxic T-cell lymphoma-4 (CTLA-4) antibody have demonstrated clinical efficacy in several advanced cancer types, including melanoma, non-small cell lung cancer, and renal cell carcinoma (Brahmer, Reckamp et al. 2015, Larkin, Chiarion-Sileni et al. 2015, Motzer, Escudier et al. 2015).

1.2.1 Single Agent PD-1 Inhibition

Anti PD-1 and PD-L1 inhibitors (eg, nivolumab and pembrolizumab) have been investigated in GC treatment and have demonstrated anti-tumor activity (Janjigian, Bendell et al. 2016, Muro, Chung et al. 2016).

Treatment with pembrolizumab achieved a 33% ORR by investigator assessment

and 22% by central data review in GC subjects with PD-L1 expressing tumors. The 6-month progression-free survival (PFS) rate was 26% and median PFS was 1.9 months (95% CI: 1.8, 3.5). The 6-month OS rate was 66% and mOS was 11.4 months (95% CI: 5.7, NR). PD-L1 expressing tumors (cutoff 1%) were reported in 40% of GC patients in this study, which is consistent with previous reports (Muro, Chung et al. 2016).

Single agent nivolumab achieved a 15% ORR in GC subjects independent of PD-L1 expression and up to 27/33% in patients with PD-L1 positivity in >1%/>5%, respectively. The 6-month progression-free survival (PFS) rate was 18% and median PFS was 1.9 months (95% CI: 1.8, 3.5). The 6-month OS rate was 49% and mOS was 5 months (Janjigian, Bendell et al. 2016).

Recently, results fo the first randomized trial in this setting were presented (Kang, Satoh et al. 2017). Nivolumab compared to placebo significantly improved overall survival (5.32 vs. 4.14 months, HR 0.63), progression free survival (HR 0.60) and overall response rate 11.2% vs. 0%. Nivolumab was well tolerated with a safety profile similar to the placebo arm.

1.2.2 Combination of PD-1 and CTLA-4 Receptor Blockade

Preclinical data indicate that the combination of PD-1 and CTLA-4 receptor blockade may improve antitumor activity (Curran, Montalvo et al. 2010). In vitro combinations of nivolumab plus ipilimumab have increased INF-γ production 2- to 7-fold over either agent alone in a mixed lymphocyte reaction. In a murine melanoma vaccine model, blockade with either CTLA-4 or PD-1 antibodies increased the proportion of CTLA-4- and PD-1-expressing CD4/CD8 tumor-infiltrating T-effector cells, and dual blockade increased tumor infiltration of T-effector cells and decreased intratumoral T regulatory cells, as compared to either agent alone.

In the Phase 1 dose escalation study CA209004, the combination of nivolumab and ipilimumab has been studied in subjects with unresectable or metastatic melanoma (Postow, Chesney et al. 2015). In this study, a safe dose level for the combination of ipilimumab and nivolumab was established for the treatment of advanced melanoma. At this dose level, 3 mg/kg ipilimumab plus 1 mg/kg nivolumab, an objective response rate of 53% was observed. This dose level has been approved in subjects with advanced melanoma in the US based on the Phase 3 study CA209067. In this study, the combination of nivolumab and ipilimumab has demonstrated increased benefit compared to either ipilimumab or nivolumab monotherapies in subjects with advanced melanoma (Larkin, Chiarion-Sileni et al. 2015).

In EGA, the open-label, multi-center Phase 1/2 study CA209032 investigated the safety and efficacy of nivolumab monotherapy or nivolumab plus ipilimumab combination therapy in multiple tumor types including GC/GEJ (Janjigian, Bendell et al. 2016). The following dose cohorts enrolled subjects with GC/GEJ cancer who had previously received at least one prior therapy, and more than 80% of subjects received more than 2 prior therapies:

- N3 monotherapy cohort: nivolumab 3 mg/kg IV every 2 weeks (n = 59)
- N1+I3 cohort: nivolumab 1 mg/kg + ipilimumab 3 mg/kg, IV every 3 weeks for 4 doses, followed by nivolumab 3 mg/kg IV every 2 weeks (n = 49);
- N3+I1 cohort: nivolumab 3 mg/kg + ipilimumab 1 mg/kg, IV every 3 weeks

for 4 doses, followed by nivolumab 3 mg/kg IV every 2 weeks (n = 52).

The results are displayed in table 1. Based on the non-randomized design no comparative efficacy can be assessed in this trial.

Clinical Activity of Nivolumab Monotherapy, and Nivolumab-plus-Ipilimumab Combination Therapy in Subjects with GC/GEJ Cancer (CA209032)			
	N3 monotherapy N=59	**N3+I1 N=52**	**N1+I3 N=49**
Population	**> 1L Prior therapy**		
Confirmed ORR, % (95% CI)	13.6 (6.0 - 25.0)	10.2 (3.4 - 22.2)	26.1 (14.3 - 41.1)
Duration of Response, mos. (95% CI)	7.1 (2.3 - 13.2)	NA (2.5 - NA)	5.6 (2.8 - NA)
PFS rate at 24 wks, % (95% CI)	17.7 (9.0 - 28.7)	8.8 (2.8 - 19.1)	23.9 (12.4 - 37.5)
Median PFS, mos (95% CI)	1.36 (1.25 - 1.51)	1.58 (1.38 - 2.6)	1.45 (1.25 - 3.94)
1-year OS rate, % (95% CI)	36 (21 - 51)	NA	34 (19 - 50)
Median OS, mos (95% CI)	5.03 (3.35 - 12.42)	4.83 (3.02 - 9.07)	6.87 (3.61 - NA)
Median length of follow-up, mos (range)	16.78 (1.86 - 24.79)	6.26 (1.07 - 13.28)	8.54 (0.93 - 12.40)

Table 1: Results of Checkmate 032 gastric cancer cohort (N3: nivolumab; 3 mg/kg; I1: ipilimumab, 1mg/kg; N1: nivolumab, 1 mg/kg: I3: ipilimumab, 3 mg/kg; ORR: objective response rate; PFS: progression-free survival; mOS:median overall survival; CI: confidence interval; 1L: first line)

The N1+I3 cohort was numerically more active in terms of ORR and survival, but resulted in a high rate of grade 3/4 toxicity of 45% (in 22 of 45 patients).

1.3 Combination of Checkpoint Inhibition and HER2 targeting Agents

The HER2 receptor antibody trastuzumab induces both, antibody dependent cytotoxicity and lymphoid infiltration in the tumor tissue (Gennari, Menard et al. 2004). Recent preclinical data demonstrated the synergistic effect of combining HER2 blockade with immunotherapy (Andre, Dieci et al. 2013, Muller, Kreuzaler et al. 2015). Muller and colleagues nicely showed the high efficacy of HER2 blockade by trastuzumab-emtansine in combination with PD-1 and CTLA4 blockade in an orthotopic breast cancer model. Thus, the combination of HER2 and PD-L1 blockade is currently investigated in several tumor types (NCT02924883, NCT02605915, NCT02649686, NCT02318901).

1.4 Combination of Checkpointinhibition with Chemotherapy and/or Molecularly Targeting Agents

The combination of checkpoint inhibitors with standard chemotherapy and/or molecular targeting agents like monoclonal antibodies (e.g. bevacizumab, necitumumab) or tyrosine kinase inhibitors of the EGF receptor or the downstream pathway (e.g. gefitinib, osimertinib, dabrafenib and trametinib) were and are currently investigated in a broad variety of different tumor entities and regimen (Bendell, Powderly et al. 2015, Creelan, Chow et al. 2015, G.R., Ramalingam et al. 2015, Melero, Berman et al. 2015, Besse, Garrido et al. 2016, Gadgeel, Stevenson et al. 2016, Langer, Gadgeel et al. 2016, Ribas, Hodi et al. 2016, Rizvi, Hellmann et al. 2016).

The available trials evaluating the combination of chemotherapy with checkpoint inhibitors have shown feasibility of the combination regimen and a safety profile expected for the individual agents (Lieu, Bendell et al. 2014, Gadgeel, Stevenson et al. 2016, Rizvi, Hellmann et al. 2016). Furthermore, the direct randomized comparison of chemotherapy with or without PD-L1 antibody has shown a similar incidence of all grade treatment related adverse events 93% (55 of 59 patients) for the combination versus 90% (56 of 62) in the chemotherapy alone group (Langer, Gadgeel et al. 2016). Recently, results of the Keynote-059 study cohort 2 have been presented showing good tolerability and high efficacy of the combination of platinum-based chemotherapy and pembrolizumab (Bang, Muro et al. 2017).

1.5 Rationale and dosing for the Experimental Combinations with Trastuzumab, Nivolumab and Ipilimumab or FOLFOX

In regard of the very limited therapeutic landscape of HER2 positive EGA (only trastuzumab licensed and trastuzumab-emtansine, recently failing) compared to breast cancer, further treatment options to relevantly improve the outcome is warranted (Thuss-Patience, Shah et al. 2017). Based on the above-mentioned proven single agent salvage activity of nivolumab, the integration of check-point inhibitors into the first line setting either within a chemotherapy-free combination arm or within an intensified standard arm of FOLFOX and trastuzumab with nivolumab may be able to improve the current limited survival of median 14 months (Bang, Van Cutsem et al. 2010, Kang, Satoh et al. 2017).

The dosing for trastuzumab is based on the current SmPC with a weekly dose of 2mg/kg either with 6mg/kg in the 3 weekly schedule or with 4mg/kg in the 2 weekly schedule. A loading dose with additional 2mg/kg (8mg/kg for the 3 weekly schedule and 6 mg/kg for the 2 weekly schedule) will be applied.

For the combination immunotherapy regimen the nivolumab 1mg/kg and ipilimumab 3mg/kg once every 3 weeks for the first 12 weeks was chosen, based on the previuos Checkmate 032 trial showing the numerically best efficacy for this regimen in this non-randomized 3 arm trial with a response rate of 26% and an OS of nearly 7 months in this already pretreated esophagogastric patient group.

The dose of nivolumab is based on the licensed dose with 3mg/kg but amended to a flat dose regimen (240mg) in either combination with FOLFOX and trastuzumab or after the initial 12 weeks in arm A incombination with trastuzumab. Nivolumab is safe and well tolerated up to 10 mg/kg every 2 weeks. Adverse events have been broadly consistent across tumor types following

monotherapy and have not demonstrated clear dose-response or exposure-response relationships. Additionally, the simulated median and 95th percentile interval of nivolumab summary exposures across body weight range (35 - 160 kg) are predicted to be maintained below the corresponding observed highest exposure experienced in nivolumab, ie, 95th percentile following nivolumab 10 mg/kg every 2 weeks from clinical study CA209003. Thus, while subjects in the lower body weight ranges would have greater exposures than 80 kg subjects, the exposures are predicted to be within the range of observed exposures at doses (up to 10 mg/kg) used in the nivolumab clinical program, and are not considered to put subjects at increased risk. For subjects with greater body weights, the simulated ranges of exposures are also not expected to affect efficacy, because the exposures predicted following administration of 240 mg every 2 weeks are on the flat part of the exposure-response curves for previously investigated tumors, melanoma and NSCLC. Given the similarity of nivolumab pharmacokinetics across tumor types and the similar exposures predicted following administration of a 240 mg flat dose compared to 3 mg/kg, it is expected that the safety and efficacy profile of 240 mg nivolumab will be similar to that of 3 mg/kg nivolumab. The 240mg flat dose regimen was FDA approved in Sep 2016.

FOLFOX will be administered applying the most commonly used modified FOLFOX6 regimen. This regimen is the current standard FOLFOX regimen in esophagogastric and colorectal cancer and is used in recent clinical trials both in the perioperative and metastatic setting (Allegra, Yothers et al. 2011, Alberts, Sargent et al. 2012, Schmoll, Cunningham et al. 2012, Schwartzberg, Rivera et al. 2014, Deng, Chi et al. 2016, Wang, Zhao et al. 2016, Yamazaki, Nagase et al. 2016, Yoon, Bendell et al. 2016, Shah, Bang et al. 2017, Venook, Niedzwiecki et al. 2017). In addition, the feasibility of the combination of mFOLFOX6 and trastuzumab or pd-1 inhibition could be shown, further supporting the choice of this regimen for the INTEGA trial (Bendell, Powderly et al. 2015, Soularue, Cohen et al. 2015).

1.6 Benefit-risk consideration of the experimental combinations

The overall outcome of esophagogastric cancer, although relevantly improving during the last decades, remains poor with a median progression free survival limited to 6-7 months and a median overall survival limited to less than 15 months with current standard doublet chemotherapy regimen and licensed antibodies (trastuzumab and ramucirumab) (Bang, Van Cutsem et al. 2010, Fuchs, Tomasek et al. 2013, Wilke, Muro et al. 2014). Intensification of standard doublet regimen resulted in very limited improvement in survival but added relevant toxicities (Van Cutsem, Moiseyenko et al. 2006). In HER2 positive disease fluoropyrimidine, platinum and trastuzumab remains the current standard of care with a limited overall survival of 14 months. Intensification of the HER2 blockade by pertuzumab in the first line situation did not improve survival in esophagogastric cancer in contrast to breast cancer (Tabernero, Hoff et al. 2017). Targeting HER2 was not efficacious in the second line setting as recently shown in the phase 3 GATSBY trial (Thuss-Patience, Shah et al. 2017). Thus, HER2 targeting is of no clinical use beyond first line and is clearly confined to the first line setting.

Thus the development of efficacious and tolerable combination regimen is urgently required particularly in the first line treatment for HER2 positive disease. The INTEGA trial will evaluate two HER2 targeting treatment strategies in the first line setting.

The experimental regimen evaluated in this trial combining the first line standard drug of trastuzumab with the currently in esophagogasric cancer furthest developed PD-1 antibody nivolumab and either the broadly tolerable and efficacious standard regimen FOLFOX or in a completely chemo-free regimen with ipilimumab. Thus, in the FOLFOX, trastuzumab and nivolumab arm patients will receive the current standard regimen of platinum-based chemotherapy with trastuzumab intensified by nivolumab, which may increase efficacy of both the chemotherapy and the HER2 blockade (refer to 1.4). Based on the currently available data an decrease in efficacy due to the investigational combination of standard first line treatment with nivolumab is unlikely. In arm A a chemotherapy-free regimen will be applied. However, arm A contains the proven efficacious trastuzumab, which is a part of the current standard first line treatment. Furthermore the combination of ipilimumab and nivolumab will be applied in arm A, which has proven efficacy in a single arm phase 2 trial (refer to 1.2.2) and may in addition be synergistic with trastuzumab (refer to 1.4). Overall, a detriment of the two experimental arms is unlikely. To account for a potential inferior efficacy of both experimental arms compared to current standard first line regimen, close meshed CT scans every 8 weeks will be conducted to detect early progression and enable immediate switch to chemotherapy or second line treatment.

The INTEGA trial may thus establish a new 1st line regimen with increased efficacy and acceptable tolerability, which need to be compared in a consecutive trial with current HER2 positive standard regimen of fluoropyrimidin, platinum and trastuzumab (Bang, Van Cutsem et al. 2010)

Based on the available data on FOLFOX in combination with PD-L1 antibodies and HER1/EGFR antibodies with PD-L1 antibodies demonstrating the feasibility and general tolerability of these two combinations, this phase II trial will start with a full dose of trastuzumab, nivolumab and either ipilimumab (dose if 3mg/kg for 4 dosese once every three weeks) or FOLFOX (according to the mFOLFOX6 regimen) (Bendell, Powderly et al. 2015, Besse, Garrido et al. 2016). To carefully evaluate potential critical toxicities patients will be closely monitored including assessments for risk of interstitial lung disease and a continuous safety analysis for every 5th patient per arm passing the 2 months assessment during the Safety Run-In Phase (first 15 patients) and every three months thereafter will be conducted (refer to 5.5.1).

From the individual patients perspective, participants may benefit from the experimental combination by improved efficacy. On the other hand, this is a novel combination trial for HER2 positive esophagogastric cancer and maybe efficacy will not be improved.

1.7 Rationale for the Translational Part

Predictive markers to tailor treatment are urgently warranted either at baseline of early during treatment.

Firstly, we will evaluate strategies to predict outcome of checkpoint inhibition by liquid biopsy immunoprofiling at baseline and shortly after initiation of treatment and correlate this with PD-L1 expression as potential response predictive biomarker. Therefore, tumor-infiltrating lymphocytes (TiL) repertoire will be determined by next-generation sequencing (NGS) of T-cell receptor beta (*TCRβ)* and immunoglobulin heavy locus (*IGH)*. Furthermore, liquid biopsy NGS-based immunoprofiling (*TCRβ* & *IGH*) will be performed prior to treatment initiation and

before the second nivolumab dose to determine response predictive immune signature (diversification pattern as read-out for ongoing immune activation, TiL clone expansion in peripheral blood). In addition, baseline FFPE will be centrally tested for PD-L1, MSI and EBV to account for further baseline markers with potential or likely predictive value for checkpoint-inhibition, although the coincidence of at least MSI and EBV with HER2 amplification is rare (Cancer Genome Atlas Research 2014, Le, Uram et al. 2015). Furthermore, CTC will be evaluated for PD-L1 status.

Resistance to HER2 targeting in HER2 positive tumors might be present upfront or will eventually develop during treatment. Several mechanisms of treatment induced have already been shown, particularly loss of HER2 amplification (Janjigian, Sanchez-Vega et al. 2016). Therefore, baseline FFPE and ctDNA will be assessed for HER2 (IHC and ISH in FFPE) and HER signaling alterations (amplifications and/or mutations in e.g. EGFR, HER2, HER3, PIK3CA). Based on previously developed techniques in breast cancer, CTCs will be evaluated for changes in HER2 status (Riethdorf, Muller et al. 2010).

2. Study Objective

The primary objective is to determine the clinical performance of ipilimumab or FOLFOX in combination with nivolumab and trastuzumab in patients with previously untreated HER2 positive locally advanced or metastatic esophagogastric adenocarcinoma in terms of overall survival.

The main secondary objective is to determine safety and tolerability, according to NCI CTC AE v4.03 and to the obtained data on vital signs, clinical parameters and feasibility of the regimen. Further secondary objectives are to determine efficacy in terms of progression free survival and objective response rate acc. to RECIST v1.1 of the experimental regimen. In addition immune response signatures (e.g. TiL repertoire and NGS immunoprofiling of immunoglobuline and T-cell receptor rearrangements), changes in HER2 and PD-L1 status in CTC and ctDNA and PD-L1 status in biopsy will be correlated with efficacy. Imaging wii be centrally review and ORR and PFS will be determined according to modified RECIST.

3. Study Design

This is a randomized, open labelled multicenter phase II trial.

3.1 Primary Endpoint

The primary endpoint is:

- Overall Survival including milestone rate @ 12 months

3.2 Secondary Endpoints

The secondary endpoints will include:

- Safety and tolerability (acc. to NCI CTC AE v4.03 and to the obtained data on vital signs, clinical parameters and feasibility of the regimen)
- Progression Free Survival (PFS) according to RECIST v1.1
- Response Rate (RR) according to RECIST v1.1
- Quality of life (EORTC QLQ-C30 and STO-22)
- Translational research (correlation of immune response signatures, changes in HER2 and PD-L1 and HER signaling status in tissue, CTC and ctDNA with efficacy
- central imaging review and determination of ORR and PFS according to modified RECIST)

4. Study Population

4.1 Number of Patients

97 patients will be enrolled in this randomized phase II trial. Patients withdrawn from the trial will not be replaced.

4.2 Selection criteria

Patients will be enrolled into the trial according to the selection criteria in section 4.2.1 and 4.2.2.

4.2.1 Inclusion criteria

1. All subjects must have inoperable, advanced or metastatic GC or GEJ carcinoma and have histologically confirmed predominant adenocarcinoma. The documentation of GEJ involvement can include biopsy, endoscopy, or imaging.
2. Subjects must have HER2-positive disease defined as either IHC 3+ or IHC 2+, the latter in combination with ISH+, as assessed locally on a primary or metastatic tumour (*Note:* Availability of formalin-fixed paraffin-embedded (FFPE) representative tumor tissue for central confirmation of HER2 is mandatory (Preferably fresh biopsy))
3. Subject must be previously untreated with systemic treatment (including HER 2 inhibitors) given as primary therapy for advanced or metastatic disease.
4. Prior adjuvant or neoadjuvant chemotherapy, radiotherapy and/or chemoradiotherapy are permitted as long as the last administration of the

last regimen (whichever was given last) occurred at least 6 months prior to randomization.

5. Subjects must have measurable or evaluable non-measurable disease as assessed by the investigator, according to RECIST v1.1 (Appendix D).
6. ECOG performance status score of 0 or 1 (Appendix B).
7. Screening laboratory values must meet the following criteria (using NCI CTCAE v.4.03):
    - WBC ≥ 2000/µL
    - Neutrophils ≥ 1500/uL
    - Platelets ≥ $100x10^3$/µL
    - Hemoglobin ≥ 9.0 g/dL
    - eGFR ≥ 30ml/min (e.g. MDRD formula, appendix G)
    - AST ≤ 3.0 x ULN (or ≤ 5.0X ULN if liver metastates are present)
    - ALT ≤ 3.0 x ULN (or ≤ 5.0X ULN if liver metastates are present)
    - Total Bilirubin ≤ 1.5 x ULN (except subjects with Gilbert Syndrome who must have a total bilirubin level of < 3.0 x ULN)
8. Males and Females, ≥ 18 years of age
9. Subjects must have signed and dated an IRB/IEC approved written informed consent form in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol-related procedures that are not part of normal subject care.
10. Subjects must be willing and able to comply with scheduled visits, treatment schedule, laboratory tests and other requirements of the study.
11. Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study drug. Women must not be breastfeeding.
12. WOCBP must use a highly effective method(s) of contraception for a period of 30 days (duration of ovulatory cycle) plus the time required for the investigational drug to undergo 5 half-lives. The terminal half-lives of nivolumab and ipilimumab are approximately 25 days and 15 days, respectively. WOCBP should use an adequate method to avoid pregnancy for approximately 5 months (30 days plus the time required for nivolumab to undergo 5 half-lives) after the last dose of investigational drug.
13. Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for a period of 90 days (duration of sperm turnover) plus the time required for the investigational drug to undergo 5 half-lives. The terminal half-lives of nivolumab and ipilimumab are approximately 25 days and 15 days, respectively. Males who are sexually active with WOCBP must continue contraception for approximately 7 months (90 days plus the time required for nivolumab to undergo 5 half-lives) after the last dose of investigational drug. In addition, male subjects must be willing to refrain from sperm donation during this time.

Notes regarding reproductive status:

Azoospermic males are exempt from contraceptive requirements. WOCBP who are continuously not heterosexually active are also exempt from contraceptive requirements, but still must undergo pregnancy testing as described in this section.

Investigators shall counsel WOCBP and male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy.

Investigators shall advise on the use of highly effective methods of contraception (see table 2), which have a failure rate of < 1% when used consistently and correctly.

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

- Hormonal methods of contraception including oral contraceptive pills (combination of estrogen and progesterone), vaginal ring, injectables, implants and intrauterine devices (IUDs)
- Nonhormonal IUDs, such as ParaGard®
- Bilateral tubal ligation
- Vasectomy (only if the vasectomized partner is the sole sexual partner of the WOCBP and the vasectomized partner has received medical assessment of the surgical success)
- Complete Abstinence (only when this is the preferred and usual lifestyle of the subject)*

*Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.

UNACCEPTABLE METHODS OF CONTRACEPTION

- Diaphragm with spermicide
- Cervical cap with spermicide
- Vaginal sponge
- Condom
- Withdrawal (coitus interruptus)
- Progestin only pills by WOCBP subject or male subject's WOCBP partner
- Periodic abstinence (calendar, symptothermal, post-ovulation methods)

Table 2 Methods of contraception

4.2.2 Exclusion criteria

1. Malignancies other than disease under study within 5 years prior to inclusion, with the exception of those with a negligible risk of metastasis or death (e.g., expected 5-year OS > 90%) treated with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, localized prostate cancer treated surgically with curative intent, ductal carcinoma in situ treated surgically with curative intent)

2. Subjects with untreated known CNS metastases. Subjects are eligible if CNS metastases are adequately treated and subjects are neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment) for at least 2 weeks prior to randomization. In addition, subjects must be either off corticosteroids, or on a stable or decreasing dose of < 10 mg daily prednisone (or equivalent) for at least 2 weeks prior to randomization.
3. History of exposure to the following cumulative doses of anthracyclines (epirubicin > 720 mg/m^2, doxorubicin or liposomal doxorubicin > 360 mg/m^2, mitoxantrone > 120 mg/m^2 and idarubicin > 90 mg/m^2, other (e.g., liposomal doxorubicin or other anthracycline greater than the equivalent of 360 mg/m^2 of doxorubicin). If more than one anthracycline has been used, then the cumulative dose must not exceed the equivalent of 360 mg/m^2 of doxorubicin
4. Baseline LVEF value < 55%, assessed by echocardiogram [ECHO], multigated acquisition (MUGA) scan, or cardiac magnetic resonance imaging (MRI) scan
5. Subjects with active, known, or suspected autoimmune disease. Subjects with Type I diabetes mellitus, residual hypothyroidism due to autoimmune thyroiditis only requiring hormone replacement, or skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment are permitted to enroll. For any cases of uncertainty, it is recommended that the medical monitor be consulted prior to signing informed consent.
6. Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids, and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.
7. Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways.
8. Persisting toxicity related to prior therapy (NCI CTCAE v. 4.03 Grade > 1); however, alopecia, sensory neuropathy Grade ≤ 2, or other Grade ≤ 2 not constituting a safety risk based on investigator's judgment are acceptable.
9. Any serious or uncontrolled medical disorder or active infection that, in the opinion of the investigator, may increase the risk associated with study participation, study drug administration, or would impair the ability of the subject to receive study drug.
10. Significant acute or chronic infections including, among others:
    - Any positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS)
    - Any positive test result for hepatitis B virus or hepatitis C virus indicating acute or chronic infection.
11. History of allergy or hypersensitivity to study drug or any constituent of the products

12. History of allogeneic tissue/solid organ transplant
13. Participation in another clinical study with an investigational product during the last 30 days before inclusion
14. Patient who has been incarcerated or involuntarily institutionalized by court order or by the authorities § 40 Abs. 1 S. 3 Nr. 4 AMG.
15. Patients who are unable to consent because they do not understand the nature, significance and implications of the clinical trial and therefore cannot form a rational intention in the light of the facts [§ 40 Abs. 1 S. 3 Nr. 3a AMG].

4.2.3 Women of Childbearing Potential

Women of childbearing potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal. Menopause is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone (FSH) level > 40 mIU/mL to confirm menopause.

*Females treated with hormone replacement therapy (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout period below are suggested guidelines and the investigators should use their judgement in checking serum FSH levels.

- 1 week minimum for vaginal hormonal products (rings, creams, gels)
- 4 week minimum for transdermal products
- 8 week minimum for oral products

Other parenteral products may require washout periods as long as 6 months. If the serum FSH level is > 40 mIU/mL at any time during the washout period, the woman can be considered postmenopausal.

5. Study Procedures and Methodology

5.1 Overall Study Schedule Overview

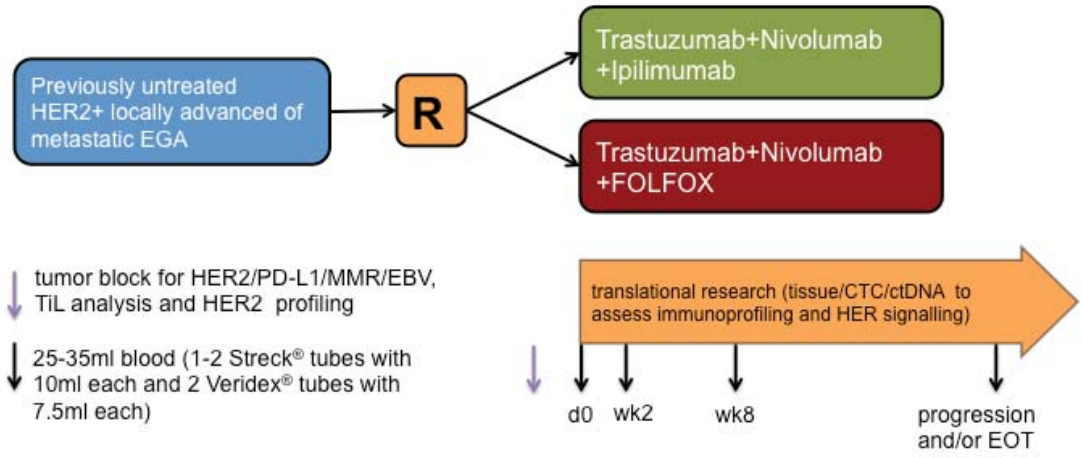


Figure 2: Overall study schedule overview

5.2 Treatment

5.2.1 Randomization

After inclusion in the treatment phase patients will be randomized to arm A or B stratified according to the following criteria

- Prior surgery of the primary tumour yes vs. no
- HER2 status IHC 3+ vs. IHC 2+ and ISH amplified

5.2.2 Investigational Product

Nivolumab and ipilimumab are not approved for treatment of EGA. The sponsor will supply both drugs. Trastuzumab, 5FU and folinic acid are approved in Germany for the treatment of EGA whereas the broadly used oxaliplatin is not approved. Trastuzumab, 5FU, folinic acid and oxaliplatin will not be supplied or reimbursed. All used agents nivolumab, ipilimumab, trastuzumab, 5FU, folinic acid and oxaliplatin will be defined as investigational medicinal product (IMP).

The IMPs (nivolumab, ipilimumab) will be supplied by the Contract Manufacturing Organization (CMO) or central pharmacy and will bear a label with the identification required by local law, the protocol number, drug identification and dosage as well as the statement "For Clinical Trial Use Only". The packaging and labeling of the study medication will be in accordance with local regulations. All the requirements of Annex 13 of the Good Manufacturing Practices guideline for labeling investigational drug will be fulfilled.

5.2.3 Dosing and schedule

All eligible patients will be randomized to

Arm A
Week 1-12
Trastuzumab 6mg/kg d1 every 3 weeks (loading dose 8mg/kg)

Nivolumab 1mg/kg i.v. d1 every 3 weeks
Ipilimumab 3mg/kg i.v. d1 every 3 weeks

Week 13 till EOT
Trastuzumab 4mg/kg d1 every 2 weeks
Nivolumab 240mg i.v. d1 every 2 weeks

Arm B
Trastuzumab 4mg/kg d1 every 2 weeks (loading dose 6mg/kg)
Nivolumab 240mg i.v. d1 every 2 weeks
mFOLFOX6 every two weeks
Oxaliplatin at a dose of 85 mg/m^2 IV over two hours (day 1)
5-FU 400 mg/m^2 IV bolus (day 1)
LV at a dose of 400 mg/m^2 iv over two hours (day 1)
5-FU at a dose of 2400 mg/m^2 IV over 46 hours (day 1-3)

Subjects may be dosed no less than 12 days (or 18 days in Arm A week 1-12) from the previous dose of drug. There are no premedications recommended for nivolumab and ipilimumab on the first cycle.

The dosing calculations should be based on the actual body weight at baseline. If the subject's weight on the day of dosing differs by > 10% from the weight used to calculate the original dose, the dose must be recalculated. All doses should be rounded to the nearest milligram. There will be no dose modifications allowed.

Subjects should be carefully monitored for infusion reactions during nivolumab, ipilimumab and trastuzumab administration. If an acute infusion reaction is noted, subjects should be managed according to protocol section 6.1.5.

5.2.4 Pretreatment

For prevention of allergic reaction an IV antihistaminic (e.g. clemastine 2mg or diphenhydramine 50mg) and paracetamol 500mg-1000mg (IV or oral) may be administered prior to trastuzumab according to local standard.

For prevention of nausea and vomiting, 5-HT3 antagonists and dexamethasone, according to local standard are strongly recommended for oxaliplatin-based chemotherapy. For delayed nausea and vomiting, the use of oral dexamethasone is recommended; metoclopramide, alizapride, prochlorperazine may be used at the discretion of the prescribing physician. Subjects should have a supply of antiemetics available at home should delayed nausea/vomiting occur.

5.2.5 Treatment duration

Treatment with trastuzumab, nivolumab and ipilimumab or FOLFOX will be administered until progression (according to RECIST v1.1), intolerable toxicity, withdrawal of consent or secondary resection. The treatment with nivolumab will be limited to a maximum of 12 months (24 applications of nivolumab). Ipilimumab will only be applied in weeks 1, 4, 7, and 10.

5.2.6 Study medication

The study medications (nivolumab and ipilimumab) will be supplied by the sponsor and delivered to the local pharmacy for preparation and administration.

Product Description and Dosage Form	Potency	Primary Packag-ing (Volume) / Label Type	Secondary Packaging (Qty) /Label Type	Appearance	Storage Conditions (per label)
Nivolumab BMS-936558-01 Solution for Injection	100 mg (10 mg/mL)	5x10 mL vial	5 vials per carton/ Open-label	Clear to opalescent colorless to pale yellow liquid. May contain particles	2 to 8°C. Protect form light and freezing
Nivolumab BMS-936558-01 Solution for Injection	1x40mg and 2x100 mg (10 mg/mL)	1x4ml and 2x10 mL vial	3 vials per carton/ Open-label	Clear to opalescent colorless to pale yellow liquid. May contain particles	2 to 8°C. Protect form light and freezing
Ipilimumab Solution for Injection	200 mg (5mg/mL)	40 mL vial	4 vials per carton/Open-label	Clear, colorless to pale yellow liquid. May contain particles	2 to 8°C. Protect from light and freezing.

Table 3 Product information

Please refer to the current version of the Investigator Brochures and/or pharmacy reference sheets for complete storage, handling, dispensing, and infusion information.
If stored in a glass front refrigerator, vials should be stored in the carton.
Recommended safety measures for preparation and handling of nivolumab and ipilimumab include laboratory coats and gloves.
For additional details on prepared drug storage and use time of nivolumab and ipilimumab under room temperature/light and refrigeration, please refer to the BMS-936558 (nivolumab) and BMS-734016 (ipilimumab) Investigator Brochure section for “Recommended Storage and Use Conditions”.

The Summary of Product Characteristics (SmPC, “Fachinformation“) for the used backbone drug (trastuzumab) will be supplied to ensure administration of drugs according to SmPC.

5.2.6.1 Handling and Dispensing

The investigator should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as per product information and the Investigator Brochure and per local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations. If concerns regarding the quality or appearance of the study drug arise, the study drug should not be dispensed and contact the sponsor immediately.

Please refer to the current version of the Investigator Brochure and/or shipment reference sheets for additional information on storage, handling, dispensing, and infusion information for BMS-936558 (nivolumab) and BMS-734016 (ipilimumab).

5.2.6.2 Destruction

Investigator drug destruction is allowed provided the following minimal standards are met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the ISF and a copy provided to the sponsor upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, ie, incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Sponsor to review throughout the clinical trial period as per the study agreement.

If conditions for destruction cannot be met, please contact the sponsor.

It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

5.2.7 Concomitant medication

5.2.7.1 Permitted therapy

Concomitant therapy includes any prescribed medications or over-the-counter preparations used by a patient between the 7 days preceding the screening evaluation and the treatment discontinuation visit.

Subjects are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Adrenal replacement steroid doses $\leq$ 10 mg daily prednisone are permitted. A brief (less than 3 weeks) course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen) is permitted. Cortison for emesis prophylaxis in the FOLFOX arm is permitted up to a maximum of 20mg dexamethasone on day 1 for acute emesis and 8mg on day 2-4 for delayed emesis. If feasible other antiemetic agent might preferentially be used for delayed emesis.
The use of full dose anticoagulants is allowed as long as the INR or aPTT is within therapeutic limits (according to the medical standard in the institution) and the patient has been on a stable dose for anticoagulants for at least two weeks at the time of registration. During treatment monitoring of INR for oral anticoagulants is recommended.

All concomitant medications should be reported to the investigator and recorded on the appropriate CRF.

5.2.7.2 Prohibited Therapy

The following medications are prohibited during the study (unless utilized to treat a drug related adverse event):

- Immunosuppressive agents
- Immunosuppressive doses of systemic corticosteroids (except as stated in Section 4.2.2 and 5.2.7.1
- Any concurrent anti-neoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, extensive, non-palliative radiation therapy, or standard or investigational agents for treatment of GC/GEJ).

Antivirals and Antiprotozoals

- Fluoropyrimidines should not be administered together with the halogenated antiviral drug sorivudine or its chemically related analogues, such as brivudine. Caution must also be exercised if metronidazole is administered.

Allopurinol

- Interactions with allopurinol have been observed for 5-FU; with possible decreased efficacy of 5-FU. Concomitant use of allopurinol with 5-FU should be avoided.

Anti-epileptic Substances

- Folinic acid may diminish the effect of anti-epileptic substances: phenobarbital, primidone, phenytoin and succinimides, and may increase the frequency of seizures (a decrease of plasma levels of enzymatic inductor anticonvulsant drugs may be observed because the hepatic metabolism is increased as folates are one of the cofactors).

The concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown.

The above list of medications is not necessarily comprehensive. The investigator should consult the prescribing information for any concomitant medication and contact the coordinating investigator or Sponsor if questions arise regarding medications not listed above.

5.3 Assessments and Guidelines for Visits

5.3.1 Baseline assessments (within 4 weeks before treatment start)

Consenting patients will have the following screening/baseline assessments performed within 4 weeks prior to the first treatment.

- Review of inclusion and exclusion criteria
- Medical and medication history, demographics physical examination including heart, chest, abdomen, skin, lymph nodes, neurological exam, inspection of accessible mucosa and height, weight, vital signs (blood

pressure, heart rate, respiratory rate, body temperature), oxygen saturation, ECOG-performance status

- Laboratory Tests:
    - Hematology panel: hemoglobin, platelets, white blood cell (WBC) count and WBC differential (neutrophils, lymphocytes)
    - Chemistry panel: sodium, potassium, calcium, magnesium, creatinine, urea, total bilirubin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total protein, albumin, LDH, glucose, amylase, lipase
    - Free T3/T4 and TSH
    - Coagulation: INR, aPTT
    - CA 72-4 (CEA, CA 19-9 optional)
    - Hepatitis B/C screening test (HBsAg, anti-HBc, anti-HBs, anti-HCV)
    - HIV screening test
    - Pregnancy test for women of childbearing potential within 24 hours prior to start of the treatment
- Blood draw (35 mL) for translational research (2 Streck® tubes with 10mL each and 2 Veridex® tubes with 7.5 mL each)
- Obtain paraffin-embedded tumor-tissue for translational research
- Echocardiography and ECG
- Quality of life assessment (EORTC QLQ-C30 and STO-22)
- Disease assessment by radiological imaging of the chest, abdomen, pelvis and all other sites of disease (CT/MRI-scan)

The investigator will confirm the patient's eligibility after all baseline scans and laboratory results have been reviewed

5.3.2 Assessments during treatment

5.3.2.1 Assessment at start of treatment and every 2 (arm B) or 3 (arm A) weeks (+3/-2 days) thereafter

The following assessments will be made previous to any new cycle. The baseline assessments may be used if within 3 days of day 1 cycle 1. Safety-relevant assessments, including pregnancy test have to be completed before dosing.

- Physical examination including heart, chest, abdomen, skin, lymph nodes, neurological exam, inspection of accessible mucosa, weight, vital signs (blood pressure, heart rate, respiratory rate, body temperature), oxygen saturation, ECOG-performance status, assessment of toxicity, concomitant medication
- Laboratory tests
    - Hematology panel: hemoglobin, platelets, white blood cell (WBC) count and WBC differential (neutrophils, lymphocytes)

- Chemistry panel: sodium, potassium, calcium, magnesium, creatinine, urea, total bilirubin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), glucose, amylase, lipase
- Free T3/T4 and TSH (every 6 weeks)
- Pregnancy test for women of childbearing potential (every 4 weeks)
- CA 72-4 (CEA, CA 19-9 optional) (only every 8 weeks, together with imaging)

- Echocardiography (every 3 months)
- Quality of life assessment (EORTC QLQ-C30 and STO-22) (every 8 weeks for 12 months afterwards every 3 months)
- Disease assessment by radiological imaging of the chest, abdomen, pelvis and all other sites of disease (CT/MRI-scan) (every 8 weeks for 12 months afterwards every 3 months)
- Blood draw (25 mL) for translational research (1 Streck® tube with 10mL each and 2 Veridex® tubes with 7.5mL each) (cycle 2 and 5)

5.3.2.2 Additional assessments during treatment with nivolumab, ipilimumab and trastuzumab in arm A until week 13 on day 12 of every cycle (+/-3 days)

- Physical examination including heart, chest, abdomen, skin, lymph nodes, neurological exam and inspection of accessible mucosa, weight, vital signs (blood pressure, heart rate, respiratory rate, body temperature), oxygen saturation, ECOG-performance status, assessment of toxicity, concomitant medication
- Laboratory tests
  - Hematology panel: hemoglobin, red blood cell (RBC) count, platelets, white blood cell (WBC) count and WBC differential (neutrophils, lymphocytes)
  - Chemistry panel: sodium, potassium, calcium, magnesium, creatinine, urea, total bilirubin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), glucose, amylase, lipase

5.3.2.3 Tumor response assessment (every 8 weeks ±7 days)

During treatment tumor response will be assessed every 8 weeks (±7 days) for up to 12 months and afterwards 3 monthly by the investigator according to RECIST v1.1 (Radiological imaging by CT and/or MRI of the chest, abdomen, pelvis and all other sites of disease). After treatment discontinuation for other than progressive disease imaging will be performed according to standard of care until progression or death. CT and/or MRI scans will be independently reviewed, thus blinded data will be collected.

5.3.2.4 Final staging (end of treatment)

The following assessments will be made if patient discontinues treatment due to progression (e.g. lack of therapeutic efficacy), severe toxicity disabling further treatment continuation or severe adverse events related to the treatment.

- Physical examination including heart, chest, abdomen, skin, lymph nodes, neurological exam and inspection of accessible mucosa, weight, vital signs (blood pressure, heart rate, respiratory rate, body temperature), oxygen saturation, ECOG-performance status, assessment of toxicity, concomitant medication
- Laboratory tests
    - Hematology panel: hemoglobin, red blood cell (RBC) count, platelets, white blood cell (WBC) count and WBC differential (neutrophils, lymphocytes)
    - Chemistry panel: sodium, potassium, calcium, magnesium, creatinine, urea, total bilirubin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total protein, albumin, LDH, glucose, amylase, lipase
    - Coagulation: INR, aPTT
    - Free T3/T4 and TSH
    - Pregnancy test for women of childbearing potential
    - CA 72-4 (CEA, CA 19-9 optional)
- Echocardiography and ECG
- Quality of life assessment (EORTC QLQ-C30 and STO-22)
- Blood draw (25mL) for translational research (1 Streck® tube with 10mL each and 2 Veridex® tubes with 7.5mL each)
- Disease assessment by radiological imaging of the chest, abdomen, pelvis and all other sites of disease (CT/MRI-scan)

5.3.3 30 days and 100 day safety follow-up (±7 days)

- Physical examination, oxygen saturation, performance status (ECOG), assessment of toxicity, concomitant medication
- Laboratory tests (hematology and chemistry panel as above), including free T3/T4 and TSH and pregnancy test for women of childbearing potential

5.3.4 Extended safety follow-up

Given the potential risk for delayed immune-related toxicities, safety follow-up must be performed every 30 days up to 100 days after the last dose of nivolumab +/- ipilimumab administration.

The extended monthly safety follow-up beyond 30 days after last study drug administration may be performed either via a site visit or via a telephone call with subsequent site visit requested in case any concerns noted during the telephone call. If there are ongoing adverse events on site visits including laboratory tests will be conducted.

5.3.5 Follow-up

All subjects will be followed every 3 months ± 28 days for up to four years after start of recruitment.

In case of progressive disease after study treatment only:

- Survival, disease status, protracted toxicity, further treatment

In any other case additionally:

- Physical examination including weight, ECOG-performance status
- Disease assessment (radiological imaging of the chest, abdomen, pelvis and all other sites of disease (CT/MRI-scan) according to standard of care
- Tumor markers (CA 72-4, optional CEA, CA 19-9) only in case of no progressive disease during or after 1st line treatment
- Blood draw (25 mL) for translational research (1 Streck® tube with 10mL each and 2 Veridex® tubes with 7.5mL each) only at progression

5.4 Study Duration

Study duration is planned as follows:
Recruitment period (counted from at least 50% of sites activated) 24 months
Follow up for primary endpoint/safety (after last patient in for a maximum of 3 months (safety follow-up 100 days) after up to 12 months of nivolumab +/- ipililmumab) 15 months
Further follow up for survival for a maximum of 48 months
(counted from first patient in)
Overall trial duration/maximum duration per individual patient 48 months

5.5 Study Termination

5.5.1 Regular Data Analysis by the Independent Date Monitoring Committee

Based on the novel combination regimen applied in this study the IDMC will monitor safety and efficacy data every 3 to 6 months throughout the trial. In addition a safety run-in phase will be conducted to detect potential safety risks early.

Safety Run-In Phase for the first 15 patients

After at least two months of treatment of the 5th, 10th and 15th patient per arm the IDMC will review the safety data respectively and decide about trial continuation.

Regular IDMC Meetings will be performed every 3 months until the last patient has passed the 2 months assessments and afterwards every 6 months to review safety data until the last administration of nivolumab.

The IDMC will propose changes, ending or continuing of the trial to the sponsor.

5.5.2 Patient Withdrawal

Patients will be withdrawn from therapy based on the following reasons:

- Post-consent determination of ineligibility based on safety criteria
- Lack of therapeutic efficacy, as evidenced by progression
- Treatment related toxicity according to dose modification criteria (section 6)
- Pregnancy
- Physician's judgment following an adverse event
- Termination by the sponsor, or a regulatory authority
- Any other reason for withdrawal that the study physician or patient indicates is in the overall best interest of the patient

Subjects who are permanently discontinued from receiving investigational product will be followed for safety unless consent is withdrawn or the subject is lost to follow-up or enrolled in another clinical study. All subjects will be followed for survival. Subjects who decline to return to the site for evaluations will be offered follow-up by phone every 6-12 weeks as an alternative.

Withdrawal of consent
The patient has the right to withdraw her/his consent any time without incurring any disadvantages.
If consent is withdrawn, the subject will not receive any further study treatment or further study observation. However, patients are requested to perform an End-of-Treatment visit. Data gathered until the day of withdrawal will be used for future analyses.
If a patient dies prior to the last scheduled study visit, the date and cause of death will be recorded.

5.5.3 Study termination

The study may be terminated by the Sponsor based on the following reasons:

- Unjustifiable risk and/or toxicity in risk-benefit analysis (decision taken by sponsor representative), e.g. when adverse events occur, unknown to date in respect of their nature, severity, duration or frequency in relation to the current established safety profile (substantial changes in risk-benefit considerations), and therefore medical and/or ethical reasons affect the continued performance of the study

- New scientific evidence becomes available during the study that could affect the patient's safety (benefit-risk analysis no longer positive), e.g. new insights from other clinical trials

- Request of the regulatory agency

- In case of difficulties in the recruitment of the planned number of subjects in the indicated time (insufficient recruitment rate)

- withdrawal of the license to manufacture

5.5.4 Study Completion

The study population will be analyzed for the primary endpoint (PFS) when 71 events have been observed. When the last patient has passed the 3 months safety assessment after completion of up to 12 months of nivolumab the final safety analyses will be conducted. Further follow up for survival will be performed for overall 4 years (counted from first patient in). The completion of the overall survival follow up will be the end of the trial.

6. Dose Modifications

6.1 General Remarks

- Toxicity will be graded according to NCI CTCAE, version 4.03 (Appendix C). Treatment modifications described below are applied according to this severity grading. Toxicities of severity grade 1 only will not lead to any dose reduction or cycle delay. The same holds for adverse reactions without any potential of serious or life-threatening complications according to the judgment of the physician (e.g. alopecia).
- Presumably, severe overlapping toxicity between trastuzumab and/or FOLFOX and the check point inhibitors (nivolumab and/or ipilimumab) will not occur. Thus, in case of toxicity requiring treatment modification, this alteration should reflect the causal relationship of the respective drug(s). For example, if the toxicity is unequivocally caused by only trastuzumab, a dosage modification of the other drugs is not required. This does not apply for nivolumab and ipilimumab, which have overlapping toxicities resulting in does modification of both drugs.
- If toxicity requires a dosing delay or interruption of any drug for more than 6 weeks, that drug should be discontinued. The patient can remain on study with the remaining drugs and will continue to be evaluated according to study procedures.
- If subject in arm A meets criteria for discontinuation of nivolumab, the subject shoud discontinue both nivolumab and ipilimumab. However, if the investigator assesses the drug-related AE to relate to ipilimumab only and not related to nivolumab, ipilimumab dosing alone may be discontinued while nivolumab dosing is delayed until subject meets criteria to resume nivolumab treatment.
- If more than one different type of toxicity occurs concurrently, the most severe grade will determine the modification.
- No dose reductions or dose escalations are permitted in this trial (besides adaptation for body weight changes)
- In case of acute allergic reactions of grade 3 or 4, the respective agent should be discontinued permanently; in case of grade 1 or 2, it is up to the physician to continue treatment without dose modification, if this is in the best interest of the patient.
- Each treatment modification or delay has to be documented in the CRF, including the respective reason.

6.1.1 Dose Delay Criteria

Because of the potential for clinically meaningful AEs, related to administration of nivolumab alone or in combination with ipilimumab, requiring early recognition and prompt intervention, management algorithms have been developed for suspected AEs of selected categories (Appendix E).

Dose delay criteria apply for all drug-related adverse events (regardless of whether or not the event is attributed to nivolumab alone or in combination with ipilimumab). All study drugs must be delayed until treatment can resume.

Administration of Nivolumab alone or in Combination with Ipilimumab should be delayed for the following:

Any Grade ≥ 2 non-skin, drug-related AE, with the following exceptions:

- Grade 2 drug-related fatigue or laboratory abnormalities do not require a treatment delay
- Any Grade 3 skin, drug-related AE

Any Grade 3 drug-related laboratory abnormality, with the following exceptions for lymphopenia, leukopenia, AST, ALT, total bilirubin, or asymptomatic amylase or lipase:

- Grade 3 lymphopenia or leukopenia does not require dose delay.
- If a subject has a baseline AST, ALT, or total bilirubin that is within normal limits, delay dosing for drug-related Grade ≥ 2 toxicity.
- If a subject has baseline AST, ALT, or total bilirubin within the Grade 1 toxicity range, delay dosing for drug-related Grade ≥ 3 toxicity.
- Any Grade ≥ 3 drug-related amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis does not require dose delay. The Investigator should be consulted for such Grade ≥ 3 amylase or lipase abnormalities.

Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

Subjects who require delay of nivolumab or nivolumab in combination with ipilimumab should be re-evaluated weekly or more frequently if clinically indicated and resume dosing when re-treatment criteria are met.

Administration of Trastuzumab should be delayed for the following:

- Asymptomatic LVEF decrease ≥ 10 percentage points from baseline and to an LVEF value of < 50%

Administration of FOLFOX should be delayed for the following:

- Absolute neutrophil count <1500/mm^3 and platelet count <100.000/mm^3
- Treatment-related diarrhea and/or abdominal cramps are not fully resolved to baseline or grade 0 and loperamide has been administered during the last 24 hours.
- Any treatment-related grade 3/4 non-hematological toxicity (except alopecia) has not yet recovered to baseline or ≤ grade 1.

6.1.2 Criteria to Resume Treatment

Subjects may resume study treatment when the drug-related AE(s) resolve to Grade ≤1 or baseline value (except alopecia), with the following exceptions:

- Subjects may resume treatment in the presence of Grade 2 fatigue
- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity
- Subjects with baseline Grade 1 AST/ALT or total bilirubin who require dose delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT OR total bilirubin
- Subjects with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters should have treatment permanently discontinued
- Drug-related pulmonary toxicity, diarrhea, or colitis, must have resolved to baseline before treatment is resumed. Subjects with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if investigator allows.
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment if investigator allows.

If the criteria to resume treatment are met, the subject should restart treatment at the next scheduled timepoint per protocol. However, if the treatment is delayed past the next scheduled timepoint per protocol, the next scheduled timepoint will be delayed until dosing resumes.

If treatment is delayed or interrupted for > 6 weeks, the subject must be permanently discontinued from study therapy, except as specified in discontinuation section.

6.1.3 Management Algorithms for Nivolumab and Ipililmumab

Immuno-oncology (I-O) agents are associated with AEs that can differ in severity and duration than AEs caused by other therapeutic classes. Nivolumab and ipilimumab are considered as an immuno-oncology agent in this protocol. Early recognition and management of AEs associated with immuno-oncology agents may mitigate severe toxicity. Management algorithms have been developed to assist investigators in assessing and managing the following groups of AEs:

Gastrointestinal, Renal, Pulmonary, Hepatic, Endocrinopathies, Skin, Neurological.

For subjects expected to require more than 4 weeks of corticosteroids or other immunosuppressants to manage an AE, consider recommendations provided in the algorithms. These algorithms are found in in Appendix E of this protocol. The guidance provided in these algorithms should not replace the Investigator's medical judgment but should complement it.

6.1.4 Guidelines for FOLFOX Dose Modifications

Patients developing toxicity related to FOLFOX will be managed according to table 4. If a grade 3 or 4 toxicity occurs after a dose reduction the patient is taken off the respective treatment, if not mentioned differently in table 4. If 5FU has to be

discontinued oxaliplatin will be stopped as well. If oxaliplatin will be discontinued e.g. due to neuropathy, 5FU may be continued.

Adverse Event	Grade	Dose modification
Neutropenia	Grade ≥ 3 or grade 4 for < 5 days	Delay/interrupt chemotherapy until resolution to grade ≤ 2 Consider use of G-CSF *3rd occurrence requiring dose delay within study:* Reduce all further doses of oxaliplatin, 5-FU and LV to 75%
	Grade 4 for ≥ 5 days or Febrile neutropenia	Reduce all further doses of oxaliplatin, 5-FU and LV to 75%
Thrombopenia	Grade ≥ 2	Delay/interrupt chemotherapy until resolution to grade ≤ 1
	Grade ≥ 3	Reduce all further doses of oxaliplatin, 5-FU and LV to 75%
	Grade 4	Discontinue treatment
Diarrhea	Grade ≥ 2	Delay/interrupt chemotherapy until diarrhea grade 0 or baseline *2nd occurrence requiring dose delays:* Delay/interrupt chemotherapy until diarrhea grade 0 or baseline and reduce 5-FU and LV to 75%
	Grade ≥ 3	Reduce all further doses of 5-FU and LV to 75%
Mucositis	Grade ≥ 2	Delay/interrupt chemotherapy until resolution to grade ≤ 1
	Grade ≥ 3 or 2nd occurrence grade ≥ 2 requiring dose delays	Reduce all further doses of 5-FU and LV to 75%
Cardiac	Any grade	Discontinue treatment if suspected to be related to 5-FU
Hand-foot-syndrome	Grade ≥ 2	Delay/interrupt 5-FU and LV until resolution to grade ≤ 1
	Grade ≥ 3 or 2nd occurrence grade ≥ 2 requiring dose delays	Reduce all further doses of 5-FU and LV to 75%
Neuropathy	Cold related dysesthesia	No dose modification
	Paresthesia / sensory neuropathy grade 1 or grade 2 persisting < 14 days	No dose modification
	Paresthesia / sensory neuropathy grade 2, persisting ≥ 14 days	Reduce all further doses of oxaliplatin to 75%.
	Paresthesia / sensory neuropathy grade 3	Delay oxaliplatin until resolution to grade 2.
Other related significant organ toxicities (except alopecia; nausea vomiting only in case of appropriate prophylaxis)	Grade ≥ 2	Delay/interrupt chemotherapy until resolution to grade ≤ 1
	Grade ≥ 3	Delay/interrupt chemotherapy until resolution to grade ≤ 1 Reduce all further doses of oxaliplatin, 5-FU and LV to 75%

Table 4 Dose modifications for chemotherapy induced toxicity

6.1.5 Treatment Infusion Reactions related to Trastuzumab, Nivolumab or Ipilimumab

Since trastuzumab, nivolumab and ipilimumab contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritis, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms of allergic-like reactions.

All Grade 3 or 4 infusion reactions should be reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE, version 4.03 (Appendix C) guidelines.

Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines as appropriate:

For Grade 1 symptoms: (Mild reaction; infusion interruption not indicated; intervention not indicated)

Remain at bedside and monitor subject until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) at least 30 minutes before additional trastuzumab, nivolumab and ipilimumab administrations.

For Grade 2 symptoms: (Moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [eg, antihistamines, non-steroidal anti inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; prophylactic medications indicated for 24 hours).

Stop the trastuzumab, nivolumab or ipilimumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen); remain at bedside and monitor subject until resolution of symptoms. Corticosteroid or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur then no further trastuzumab, nivolumab and ipilimumab will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded on the electronic case report form (eCRF). The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) should be administered at least 30 minutes before additional trastuzumab, nivolumab and ipilimumab administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.

For Grade 3 or Grade 4 symptoms: (Severe reaction, Grade 3: prolonged [ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [eg, renal impairment, pulmonary infiltrates]). Grade 4: (life threatening; pressor or ventilatory support indicated).

Immediately discontinue infusion of trastuzumab, nivolumab or ipilimumab. Begin an IV infusion of normal saline, and treat the subject as follows. Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. Trastuzumab, nivolumab or ipilimumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms.

In the case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritis within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine, or corticosteroids).

6.1.6 Algorithm for Continuation or Discontinuation of Trastuzumab Based on LVEF Assessments

There is a risk of cardiac dysfunction with trastuzumab. A decrease in LVEF has been observed in patients receiving trastuzumab; however, the majority of patients show improvement or return to baseline function on follow up. Monitoring of LVEF is required while patients are receiving trastuzumab as well as after completing therapy as per SmPC.

If symptomatic LVSD symptoms develop or there is a confirmed LVEF decrease (LVEF decrease ≥ 10 percentage points from baseline and to an LVEF value of < 50%), the patient must discontinue trastuzumab (refer to figure 3). Symptomatic LVSD (CHF) should be treated and monitored according to standard medical practice. These patients should be evaluated by a certified cardiologist, and the results of this evaluation should be reported on the eCRF.

Figure 3 summarizes the management of study treatment for patients who have an asymptomatic decrease in LVEF (LVEF decrease ≥ 10 percentage points from baseline and to an LVEF value of < 50%). The decision whether to continue or stop study treatment should be based on two factors: measured LVEF value and change in LVEF value from baseline according to the algorithm.

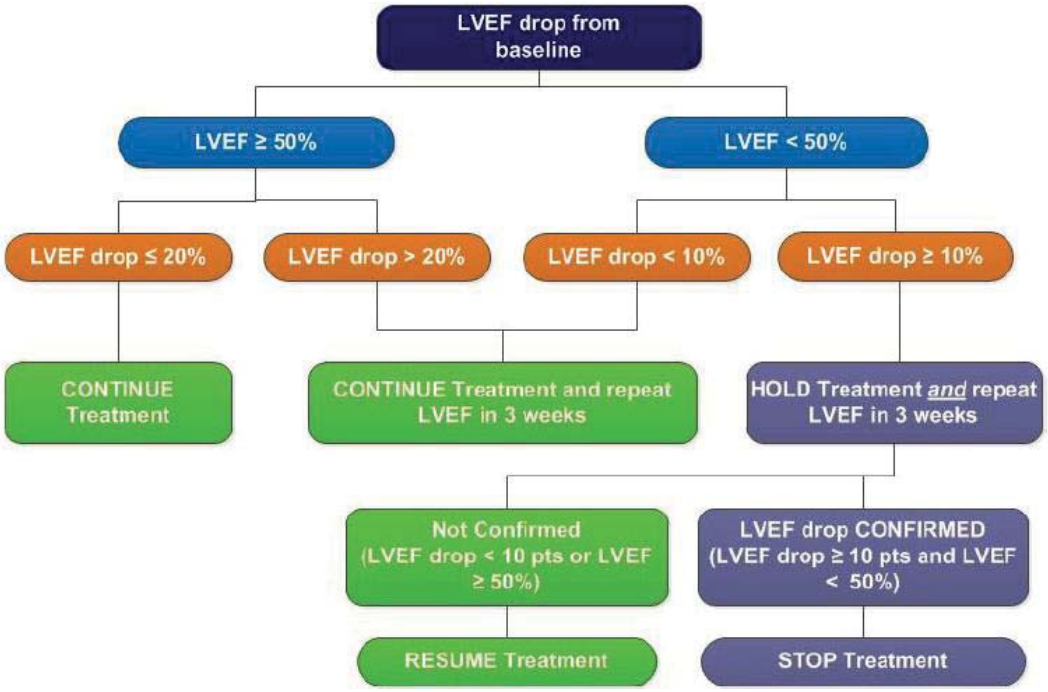


Figure 3 Algorithm on management of trastuzumab treatment in case of asymptomatic LVEF drop from baseline.

6.1.7 Discontinuation Criteria

Nivolumab and ipilimumab should be permanently discontinued for the following:

- Any Grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment
- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days, with the following exceptions for drug-related laboratory abnormalities, uveitis, pneumonitis, bronchospasm, hypersensitivity reactions, and infusion reactions, and endocrinopathies:
    - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
    - Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation
    - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except those noted below
        - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
        - Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
            - AST or ALT > 8 x ULN
            - Total bilirubin > 5 x ULN

- Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN

- Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events which do not require discontinuation:
    - Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis and decrease to < Grade 4 within 1 week of onset.
    - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
    - Grade 4 lymphopenia or leucopenia
    - Grade 4 drug-related endocrinopathy adverse events, such as adrenal insufficiency, ACTH deficiency, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the Investigator.
- Any dosing interruption lasting > 6 weeks with the following exceptions:
    - Dosing delays or interruptions to allow for prolonged steroid tapers to manage drug-related adverse events are allowed. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the Coordinating Investigator must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted or delayed
    - Dosing interruptions or delays lasting > 6 weeks that occur for non-drug-related reasons may be allowed if approved by the Coordinating Investigator. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the Coordinating Investigator must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued nivolumab and ipilimumab dosing

Trastuzumab should be permanently discontinued for the following:

- Development of symptomatic left ventricular systolic dysfunction (LVSD) symptoms or confirmed left ventricular ejection fraction (LVEF) decrease (LVEF decrease ≥ 10 percentage points from baseline and to an LVEF value of < 50%) (refer to figure 3)

FOLFOX should be permanently discontinued

- According to the dose modification guidelines displayed in 6.1.4

7. Criteria of Evaluation

7.1 Overall Survival (OS)

Overall survival will be determined as time from the randomization date to the date of death. A subject who has not died will be censored at last known date alive.

7.2 Progression Free Survival (PFS)

Time from randomization to the date of first observed disease progression (investigator assessment according to RECIST 1.1) or death from any cause. Clinical deterioration in the absence of unequivocal evidence of progression (per RECIST 1.1) is not considered progression for purposes of determining PFS. Subjects who die without a reported prior progression will be considered to have progressed on the date of their death. Subjects who did not progress or die will be censored on the date of their last evaluable tumor assessment. Subjects who did not have any on study tumor assessments and did not die will be censored on the date they were registered. Subjects who started any subsequent anti-cancer therapy without a prior reported progression will be censored at the last evaluable tumor assessment prior to or on the date of initiation of the subsequent anti-cancer therapy.

7.3 Response Rate (RR)

Response rate will be assessed according to RECIST v1.1. Overall response rate will be defined as the proportion of randomized subjects with best response of complete or partial reponse.

7.4 Safety Endpoints

Safety assessments will include physical examinations including vital signs (blood pressure, heart rate, respiratory rate), performance status (ECOG), clinical laboratory profile, concomitant medication and adverse events.
All observed toxicities and side effects will be graded according to NCI CTCAE v4.03 (NCI 2009) for all patients and the degree of association of each with the procedure assessed and summarized.
Treatment related serious adverse events rate (SAE) will be determined.

7.5 Quality of life assessment (EORTC QLQ-C30 and STO-22)

Quality of life will be assessed using the EORTC QLQ C30 questionnaire and the module STO22 at baseline, during treatment every 8 weeks during the first 12 months, afterwards every 3 months and at the end of treatment. Assessments in parallel to tumor assessments until radiologic disease progression.

8. Translational research

8.1 Translational research projects

The following translational research is currently planned, but may be adapted taking into account new research data

- Tumor-infiltrating lymphocytes (TiL) repertoire determination from tumor
- Liquid biopsy next-generation sequencing (NGS) immunoprofiling (*TCRβ* & *IgH*) before treatment initiation and before second cycle to determine

response predictive immune signature (diversification pattern as read-out for ongoing immune activation, TiL clone expansion in peripheral blood)

- In addition FFPE will be centrally tested for PD-L1, HER2 (IHC and ISH), MSI, EBV and HER signaling alterations (amplifications and/or mutations in e.g. EGFR, HER2, HER3, PIK3CA) and correlated with clinical efficacy.
- CTC will be evaluated for changes in HER2 and PD-L1 status
- ctDNA will be evaluated for HER signaling alterations (amplifications and/or mutations in e.g. EGFR, HER2, HER3, PIK3CA)
- Central imaging review and determination of ORR and PFS according to modified RECIST (refer to appendix D).

8.2 Sampling time points and materials

The tumor block for TiL analysis, HER2, PD-L1 and HER signaling assessment will be obtained at baseline. Blood (45mL; 3 Streck® tubes with 10mL each and 2 Veridex® tubes with 7.5mL each) will be collected prior to first treatment and beginning of cycle 2 and 5 and at progression and/or end of treatment. In addition, imaging will be retrospectively collected.

For tissue and blood sampling working instructions refer to appendix F. Additional translational research working instruction will be supplied to the sites.

8.3 Usage of translational data

Upon receipt in the central laboratory the obtained blood will be separated into leucocytes and plasma and stored together. Leucocytes, plasma and the obtained tissue will be stored in the central laboratory until the preplanned analysis will be conducted when the clinical data from the trial are available. Further storage for up to 15 years from first patient in is intended to enable future evaluation of leucocyte, plasma or tissue based markers relevant for the further development of combination regimen with checkpoint inhibitors, chemotherapy and EGFR targeting drugs.

9. Assessment of Adverse Events & Safety Reporting

Adverse event reporting summary

It is the responsibility of the investigators to record all adverse events in the eCRF. Any serious adverse event (SAE, irrespective of suspected causal relationship) which occurs after the patient has given written informed consent and up to the end of the safety follow-up period (100 days after last dose) must be reported in writing within 24 hours after site awareness to the CRO.

Reports have to be sent via fax to:

Dr. Notghi Contract Research GmbH

Beuthstraße 7

10117 Berlin

Tel. 030 526828095

Fax 030 526828096

E-Mail: aio.drugsafety@notghi.com

9.1 Independent Data Monitoring Committee (IDMC)

An independent data monitoring committee will follow the progress of the clinical trial, evaluate the safety parameters and will propose changes, ending or continuing of the trial to the sponsor. The planned close meshed toxicity analysis after the 5th, 10th and 15th patient per arm passing the 2 months assessment and every 3 months thereafter until the last patient passing the 2 moths assessments and every 6 months afterwards until the last patient discontinues nivolumab treatment will be performed by the IDMC with the data collected and prepared by the CRO.

9.2 Reference safety documents

The current versions of the Investigators' Brochure (IB) of nivolumab and ipilimumab as well as a current SmPC of trastuzumab, 5FU, leucovorin and oxaliplatin will be used as reference documents and will be provided to the investigators in the Investigator's Site File.

9.3 Adverse Events Definitions

9.3.1 Adverse Event

An adverse event (AE) is defined in the International Conference on Harmonization (ICH) Guideline for Good Clinical Practice as "any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment." (ICH E6: section 1.2).

An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product.

Worsening of a pre-existing medical condition (e.g. diabetes, migraine headaches, gout) should be considered an adverse event if there is either an increase in severity, frequency, or an association with significantly worse outcomes.

Interventions for pre-treatment conditions (e.g. elective cosmetic surgery) or medical procedures that were planned before study enrolment are not considered adverse events.

9.3.2 Serious Adverse Event

A serious adverse event (SAE) is defined as any untoward medical occurrence (adverse event) that at any dose:

- results in death,
- is life-threatening (subject was at immediate risk of death at the time of the event),
- requires in-patient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,

- is a congenital anomaly / birth defect or,
- any other significant medical condition.

A hospitalization meeting the regulatory definition for “serious” is any inpatient hospital admission that includes a minimum of an overnight stay in a health care facility. Any adverse event that does not meet one of the definitions of serious i.e. important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require interventions to prevent one of the other outcomes listed above (e.g. emergency room visit, outpatient surgery, or requires urgent investigation) may be considered by the investigator to meet the “other significant medical condition” criterion for classification as a serious adverse event. Examples include allergic bronchospasm, convulsions, and blood dyscrasias.

Hospitalization for performing of protocol-required procedures or administration of study treatment or hospitalizations for procedures planned prior to study start and elective hospitalizations are not classified as an SAE.

Progression of the underlying malignant disease and symptoms caused by progression of the underlying tumor disease need not to be reported as SAE in this protocol, unless progression or symptoms of progression are assessed as causally related to study medication.

9.3.3 Other reportable events

The following events are reportable and must be handeled as SAEs:

- Is a new cancer (that is not a condition of the study);
- overdose: An overdose is defined as a subject receiving a dose of IMP in excess of that specified in the Investigator’s Brochures nivolumab and Ipilimumab/ SmPCs for other IMP, unless otherwise specified in this protocol.
- pregnancy
- Transmission of an infectious agent via medicinal product
- Drug induced liver injury defined as follows:
  - ALT or AST elevation > 3 times upper limit of normal (ULN)

  AND

  - Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),

  AND

  - No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

9.3.4 Unexpected Adverse Event

An unexpected adverse event is any adverse drug event, the specificity or severity of which is not consistent with the current version of the Investigators’ Brochure of the IMPs or the repective SmPC as applicable. Also, reports which add significant information on specificity or severity of a known, already documented adverse event constitute unexpected adverse events. An event

more specific or more severe than described in the current version of the Investigators' Brochure of the IMPs or the repective SmPC (as applicable) would be considered "unexpected".

A suspected unexpected serious adverse reaction (SUSAR) is a serious adverse reaction, the nature, or severity of which is not consistent with the applicable safety reference document (current IB or SmPC). All suspected adverse reactions related to the study medication which occur in the concerned trial and that are both unexpected and serious (SUSARs) are subject to expedited safety reporting.

9.4 Assessment of relationship - Adverse drug reaction

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The causal relationship can be one of the following:

- **Related:** There is a reasonable causal relationship between study drug administration and the AE.
- **Not related:** There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

In case of a missing causality assessment in the eCRF or SAE reporting form, the event will be regarded as "related" unless further specified.

A serious ADR (SADR) is an adverse drug reaction that meets the definition of a serious event (provided above).

9.5 Assessment of severity

Intensity of adverse events will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.03.
If an adverse event occurs which is not contained in the CTCAE version 4.03, the five-point scale below will be used.

Grade 1:	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2:	Moderate: minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL
Grade 3:	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
Grade 4:	Life-threatening consequences; urgent intervention indicated
Grade 5:	Death related to AE

9.6 Safety recording and reporting requirements

9.6.1 Recording periods

- *Non-serious* and *serious adverse events* are recorded continuously from time of signed informed consent until 100 days after last dose of IMP.

- *Other reportable events* are continuously recorded from time of signed informed consent until 100 days after last dose of IMP.
- Pregnancies occurring in a study subject are recorded from time of signed informed consent until **5 month** after last dose of IMP. Pregnancies occurring in a partner of a study subject are recorded from time of signed informed consent until **7 month** after last dose of IMP.

9.6.2 Recording and Reporting requirements

Adverse events: The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by patient are properly captured in the patients' medical records.
Adverse events will be recorded in the AE page of eCRF using a recognized medical term or diagnosis that accurately reflects the event. Adverse events will be assessed by the investigator for severity, relationship to the investigational product, possible etiologies, and whether the event meets criteria of an SAE or other reportable event (as per section 9.3.3) and therefore requires expedited reporting.

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- Changes in NCI CTCAE grade and the maximum CTC grade attained
- Whether the AE is serious or not
- Investigator causality rating against IMPs (nivolumab, ipilimumab, trastuzumab, 5FU, leucovorin, oxaliplatin; yes or no)
- Action taken with regard to IMP:
    - none
    - study drug temporarily interrupted
    - study drug dose modifications
    - study drug permanently discontinued.
- Outcome:
    - recovered/resolved
    - recovered/resolved with sequelae
    - not recovered/not resolved
    - fatal
    - unknown (only applicable if patient is lost to follow-up);

In addition, the following variables will be collected for SAEs as applicable:

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- Seriousness criterion
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Description of AE

- Causality assessment in relation to other Study procedure(s)

Serious adverse events:

- For each patient any adverse event or abnormal laboratory test value that is serious occurring during the course of the study must be reported immediately (within 24 hours / GCP-V § 12(4)) after awareness to the CRO via fax utilizing a completed SAE Report Form.

- Serious Adverse Events that are **unexpected** and **considered related** to IMP and occur **after the completion of the trial** should be reported to the sponsor (AIO-Studien-gGmbH) within one working day [ICH E2A III.E.3].

Other reportable events:

- For each study subject any adverse event that fulfils the criteria in section 9.3.3 occurring during the course of the study must be reported immediately (within 24 hours) after awareness to the CRO via fax utilizing a completed SAE Report Form.
- Overdose: Any overdose of a study subject with any of the IMPs, with or without associated AEs/SAEs, must be reported immediately (within 24 hours) after awareness to the CRO via fax utilizing a completed SAE Report Form.
- If the overdose results in an AE, the AE must also be recorded as an AE. Overdose does not automatically make an AE serious, but if the consequences of the overdose are serious, for example death or hospitalization, the event is serious and must be recorded and **reported** as an SAE.

Pregnancies:

- Pregnancies occurring in a study subject or partner of a study subject are reported **within 24 hours** of knowledge of the event to the CRO using the Pregnancy Report Form.
  Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form. See section 9.7.6 for further details.
- If an SAE is experienced in addition to or related to the pregnancy e.g. an induced or spontaneous abortion, also an SAE Report has to be sent to the CRO within 24 hours of first knowledge.

Abnormal laboratory results:
In general it is the investigator's responsibility to review all abnormal laboratory results and to determine if a given value represents a clinically significant change compared to previously obtained values and results in an Adverse Event or not.

- Abnormal laboratory test results will be recorded on the laboratory results pages of the eCRF. Laboratory-test-value abnormalities should additionally be considered an AE in case they are:
  1. Accompanied by clinical symptoms

2. Leading to a change in study medication (e.g. dose modification, interruption or permanent discontinuation)
3. Requiring a change in concomitant therapy (e.g. addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy or treatment)

- Any laboratory result abnormality fulfilling the criteria for a serious adverse event (SAE) should be reported as such, in addition to being recorded as an adverse event in the eCRF.

9.6.3 Sponsor obligations

The Sponsor and the CRO will ensure compliance with all regulatory reporting requirements including the notification of the appropriate Ethics Committees, Competent Authority and participating investigators of all serious adverse events occurring at the sites in accordance with national law, ICH Good Clinical Practice and European / EMA requirements.

- A Sponsor representative (e.g. CRO or medical expert) will medically review all SAE reports and perform the expectedness assessment.
- A Sponsor representative (e.g. CRO) will forward SAE, Other reportable events and pregnancy reports within one working day to the Coordinating Investigator (CI/LKP) and BMS.
- Every SAE, being assessed by either the investigator or the Sponsor as suspected to be related to IMP und assessed as being either unexpected or unexpected with regard to outcome or severity of the event will be reported by the Sponsor as SUSAR to the competent authority, responsible ethics committee and investigators of the trial in line with the national regulations in effect (German drug law [AMG] and GCP-V § 13).
    - Fatal or life-threatening SUSARs must be reported as soon as possible, but no later than 7 days; further important information to these cases may be reported as follow-up within additional 8 days. All others SUSARs have to be reported no later than 15 days. BMS will be notified in parallel.
    - Also all adverse events which can change the benefit-risk ratio of the study drugs or otherwise fulfil the criteria outlined in GCP-V §13 Abs.4 have to be handled/reported as SUSARs. BMS will be notified in parallel.

9.7 Handling of Safety Parameters

9.7.1 Adverse events

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)
It will be left to the investigator’s clinical judgment to determine whether an adverse event is related and of sufficient severity to require the subject’s removal from treatment or from the study. A subject may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable adverse event. If

either of these situations arises, the subject should be strongly encouraged to undergo an end-of-treatment assessment and be under medical supervision until symptoms cease or the condition becomes stable.

9.7.2 Treatment and Follow-up of Adverse Events

During the course of the study all AEs and SAEs should be proactively followed up for each subject. Every effort should be made to obtain a resolution for all events, even if the events continue after discontinuation/study completion. The investigator is responsible for following all SAEs until resolution, until the subject returns to baseline status, or until the condition has stabilized with the expectation that it will remain chronic, even if this extends beyond study participation.

9.7.3 Follow-up of Abnormal Laboratory Test Values

In the event of unexplained abnormal laboratory test values, the tests should be repeated immediately and followed up until they have returned to the normal range and/or an adequate explanation of the abnormality is found. If a clear explanation is established it should be recorded on the eCRF.

9.7.4 Overdose

The investigator will use clinical judgment to treat any overdose.

9.7.5 Drug induced liver injury

Drug-induced liver injury is under constant surveillance by sponsors and regulators and is considered a protocol-specified adverse event (Other reportable event). Timely detection, evaluation, and follow-up of laboratory alterations of selected liver laboratory parameters to distinguish an effect of the investigational drug from other causes are important for patient safety and for the medical and scientific interpretation of the finding.

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event.

Study subjects showing laboratory abnormalities as defined in section 9.3.3. need to be followed up until the protocol specific retreatment criteria have been met and according to 6.1.2 of this clinical trial protocol.

9.7.6 Pregnancies and contraception

Reproductive status

For this trial, male subjects will be considered to be of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

Female subjects will be considered of non-reproductive potential if they are either:

(1) postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women < 45 years of age a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.);

OR

(2) have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening;

OR

(3) has a congenital or acquired condition that prevents childbearing.

Counseling of study subjects and partners:

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study subjects of childbearing potential must adhere to the contraception requirements (see section 4.2.1). If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

- Maternal exposure: Women of childbearing potential (WOCBP) must use appropriate method(s) of contraception. *WOCBP should use an adequate method to avoid pregnancy for 5 months after the last dose of nivolumab, ipilimumab and trastuzumab*. A female patient must be instructed to immediately inform the investigator if she becomes pregnant during the study. Monitoring of the patient should continue until conclusion of the pregnancy.
- Paternal exposure: Men who are sexually active with WOCBP must use any contraceptive method with a failure rate of less than 1% per year. Men receiving IMPs and who are sexually active with WOCBP will be instructed to adhere to contraception for a period of 7 months after the last dose of investigational products. Male subjects must refrain from donating sperm during the study and for 7 month after the last dose of nivolumab and ipilimumab. A male study subject must be instructed to immediately inform the investigator if a pregnancy occurs in his partner during the study and up to 7 month after last dose of IMP.

Pregnancies

Pregnancy itself, or pregnancy of a subject's partner, is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of any conception occurring from the date of the first dose until 5 months (female subjects) or 7 month (partners of male subjects) after the last dose (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the subject was withdrawn from the study.

Subjects who become pregnant during the study period must not receive additional doses of investigational product but will not be withdrawn from the study until the necessary safety follow-up has been completed. The investigator should counsel the subject; discuss the risks of continuing the pregnancy, and possible effects on the fetus. The pregnancy will be followed for outcome of the

mother and child (including any premature terminations) and should be reported to the CRO, which will notify the sponsor and BMS or designee after outcome.

Pregnancy of a subject's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) occurring from the date of the informed consent 7 month after the last dose should, if possible, be followed up and documented. The investigator should counsel the subject's partner; discuss the risks of continuing the pregnancy, and possible effects on the fetus.
Where a report of pregnancy is received, prior to obtaining information about the pregnancy, the Investigator must obtain the consent of the subject's partner. Sponsor will provide a partner ICF in line with local procedures and submit it to the relevant Ethics Committees (ECs)/Institutional Review Boards (IRBs) prior to use.

9.7.7 Adverse Drug reactions with Concomitant Medication

The investigators must be aware that for all concomitant medications the regulations of post marketing reporting for suspected adverse drug reactions apply, i.e. reporting to the marketing authorization holder or the local regulatory bodies.

10. Data Analysis and Statistical Considerations

10.1 Sample Size Calculation

The present trial is designed as a randomized phase II study, which aims to estimate the therapeutic efficacy of two experimental regimen. OS analysed according to the ITT principle is the primary efficacy endpoint. The efficacy assumptions on the current standard-of-care treatment are derived from historical data.

The TOGA trial has defined the standard 1st line treatment with chemotherapy and trastuzumab with a 12-month-OS rate (OSR@12) of 55% (median OS of 13.8 months) (Bang, Van Cutsem et al. 2010). Nivolumab in chemotherapy refractory patients (median 3 prior treatment lines) results in an overall response rate of 11-14% and a median OS of about 5.3 months (Janjigian, Bendell et al. 2016, Kang, Satoh et al. 2017). The combination of nivolumab and ipilimumab in the same patient population results in an overall response rate of 26% and a median OS of about 6.9 months (Janjigian, Bendell et al. 2016).

The INTEGA trial will evaluate two experimental regimen in 1st line HER2 positive EGA treatment, a chemo-free regimen with trastuzumab+nivolumab+ipilimumab and a intensified TOGA-like regimen with trastuzumab+nivolumab+FOLFOX. Each of the experimental arms would be considered promising, if the true 12-month-OS rate amounts to 70 %. This translates into a hazard ratio of 0.6 compared to the standard OSR@12 of 55% for chemotherapy and trastuzumab.

Based on these assumptions, and an exponential shape of the survival curves, a one-sided logrank test with a sample size of 41 subjects achieves 80% power at a one-sided significance level of 0.05 to detect a hazard ratio of 0.6 when the proportion surviving with the current standard is 0.55 (OSR@12 months). Overall 82 patients will be included and randomized into the two experimental arms (41 in

each experimental treatment group). The rate of drop-outs is estimated to be 15%. Hence, the total number of subjects to be recruited is N= 97. This calculation assumes an accrual time of 24 months, and a minimum follow-up of 15 months of all patients alive at the time point of analysis. The sample size is derived according to the method described by J Wu (Pharmaceut Stat 2015, 14:26-33).

Randomization will be performed according to the following stratification criteria:

- Prior surgery of the primary tumour yes vs. no
- HER2 status IHC 3+ vs. IHC 2+ and ISH amplified

10.2 Populations for Analysis

All patients receiving at least one dose of study treatment will be evaluable for safety and included in the safety population.
The Intention-to-treat (ITT) population will include all randomized patients in the study (signed ICF and confirmation of eligibility).

10.3 Patient Demographics/Other Baseline Characteristics

The following demographic and baseline characteristics will be summarized descriptively by treatment group:

- Gender and age
- ECOG performance status
- Tumor marker
- Disease status
- Molecular background (PD-L1, MSI, EBV)
- Other characteristics (e.g liver chemistry)

Medical history will be summarized by primary body system organ class and preferred term.

10.4 Treatments (study treatments)

The number and dose of treatment cycles will be summarized by treatment group.

10.5 Efficacy Analysis

10.5.1 Primary Efficacy Endpoint

Overall Survival including milestone rate @ 12 months.

Time to event distributions will be estimated using Kaplan-Meier techniques. Median OS along with 95% CI will be constructed based on a log-log transformed CI for the survivor function. Rates at fixed timepoints (e.g. milestone rate of OS at 12 months) will be derived from the Kaplan-Meier estimate and corresponding confidence interval will be derived based on Greenwood formula for variance derivation and on log-log transformation applied on the survivor function.

For the analysis of the primary endpoint and hypothesis testing a total of 44 events need to be observed. Hypothesis testing will be performed with a one-sided logrank test (against a constant hazard derived from the historical data on the standard therapy, cf. section 10.1) at a one-sided significance level of 0.05.

10.5.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints will be the following variables:

- Safety and tolerability (acc. to NCI CTC AE v4.03 and to the obtained data on vital signs, clinical parameters and feasibility of the regimen)
- Progression Free Survival (PFS) according to RECISTv1.1
- Response Rate (RR) according to RECIST v1.1
- Quality of life assessment (EORTC QLQ-C30 and STO-22)
- Translational research (including central and retrospective RR and PFS according to mRECIST)

For the time-to-event variables PFS and OS, the Kaplan-Meier method will be used and treatment groups or subgroups may be compared using a logrank test. All resulting p-values for secondary endpoints will be considered descriptive and no p-value adjustment for multiple testing will be performed.

Response rate, safety and tolerability will be documented in a descriptive way. Continuous variables will eventually be compared using t tests or Wilcoxon tests, and categorical variables using a chi-square test or test for trend, as appropriate.

All secondary efficacy analyses, excluding toxicity, which will be based on the safety population, will be based on the ITT population.

Further details on the analyses will be described in a Statistical Analysis Plan.

10.5.3 Safety analyses (toxicity)

Data from all subjects who receive one or more doses of study treatment will be incorporated into the safety analyses. Study treatment exposure will be summarized. Adverse events, vital sign measurements, ECOG performance status, clinical laboratory information, and concomitant medications will be tabulated and summarized by group. All toxicities will be summarized by relative and absolute frequency, and maximum severity grade by category based on the CTCAE Version 4.03. Serious adverse events (SAE) will be listed separately. Safety information obtained during the follow-up period during each segment will be incorporated into these analyses. Graphical displays will be provided where useful in the interpretation of results.

11. Data management

11.1 Randomization Procedure

Randomization to study treatment should occur within seven days after eligibility criteria have been met. Upon confirmation of eligibility, study subjects will be randomized centrally to arm A (trastuzumab, nivolumab and ipilimumab) or B (trastuzumab, nivolumab and FOLFOX) in 1:1 ratio, according to the above mentioned stratification factors.

11.2 Patient identification list

All included patients have to be documented in a confidential patient identification list. This list contains the patient specific numbers (patient- and randomization-number) together with date of birth and the full name of the patient. Patient

related data will be just transmitted in pseudonymized form. The identification list will stay at each center.

11.3 Data capture

All data will be entered directly at the center by the site staff with remote data entry (RDE). A study-management software will be used for data capture and query management. Automatic edit checks will validate data directly during entry into the study database. Data will be evaluated for consistency, accuracy and completeness regularly. After completion of data capture data-base will be closed and the data will be transferred into the statistic software.

12. Quality assurance

12.1 Standardization

Criteria for assessing efficacy and safety endpoints will be standardized by using NCI-CTCAE Version 4.03 for safety issues, RECIST Version 1.1 and irRECIST for efficacy parameters. Every center has to reveal their laboratory norm values and their validation through certification.

12.2 Data access

All source data have to be in the patients file under the responsibility of the investigator. Documentation in the eCRF must correspond to source data in the patient file. For this trial source data are defined as:

- medical and demographical data
- results of laboratory and imaging data
- selection criteria
- signed informed consent form (original)
- EORTC QLQ-30 and EORCT QLQ-STO-22

12.3 Monitoring/ Source Data Verification (SDV)

The monitoring will be conducted according to local requirements.

Monitoring will be performed by the CRO’s monitors. The study monitor will review the CRF data for completeness and accuracy during the monitoring visits (source data verification / SDV). The study monitor will point out any discrepancies between source data and the data captured in the CRF. The monitor will issue electronic queries to site staff to initiate discrepancy resolution. Discrepancies which require CRF data corrections have to be re-solved by authorized site personnel by answering these monitoring queries.
The frequency of on-site visits will depend on the number of recruited patients. The monitor must be given access to subject medical records and other study-related records needed to verify the entries on the CRF. The investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing case report forms, are resolved. The investigator has to ensure that all data required according to this protocol will be entered promptly in the CRF.

Quality control of data will be done by reviewing the data entered into the trial software for consistency, accuracy and completeness. During on-site visits the correct transmission of data into the CRF (source data verification) as well as

informed consent forms, selection criteria, efficacy and safety parameters will be reviewed. The complete scale of the monitoring will be defined by the trial specific monitoring plan.

12.4 Audits and Inspections

To ensure quality of data, study integrity, and compliance with the protocol and the various applicable regulations and guidelines, the sponsor may conduct site visits to institutions participating to protocols.
The investigator, by accepting to participate to this protocol, agrees to co-operate fully with any quality assurance visit undertaken by third parties, including representatives from the sponsor, national and/or foreign regulatory authorities or company supplying the product under investigation, as well as to allow direct access to documentation pertaining to the clinical trial (including CRFs, source documents, hospital subject charts and other study files) to these authorized individuals.
The investigator must inform the sponsor immediately in case a regulatory authority inspection will be scheduled.

13. Regulatory and Legal Obligations

13.1 General provisions/Declaration of Helsinki

This study is conducted in agreement with the ICH Harmonized Tripartite Guideline on Good Clinical Practice, valid since 17.01.1997, the Declaration of Helsinki (in its current version) and the respective national laws (in its current version). The Principle Investigator has more than two years of experience in the conduction of clinical drug trials.

13.2 Patient Protection

The responsible investigator will ensure that this study is conducted in agreement with either the Declaration of Helsinki (in its current version) or the laws and regulations in its current version.
The protocol has been written, and the study will be conducted according to the ICH Harmonized Tripartite Guideline for Good Clinical Practice (reference: http://www.ifpma.org/pdfifpma/e6.pdf). The protocol will be approved by Independent Ethics Committees.

13.3 Competent authority

Prior to the start of the trial an application for authorization by the competent Higher Federal Authority is submitted by the sponsor including a copy of the protocol and other information and documents required by the competent national Higher Federal Authority. A copy of the written approval must be available before the start of recruitment of subjects into the study. All changes of the study protocol or other study document classified “substantial” as well as adverse events will be announced to the CA (according to the appropriate Directives and national legal requirements). Once a year or whenever it is questioned the CA will get information about all SAR and about the security of the affected subjects, according to the appropriate Directives and national legal requirements. Recommendations and tips of the CA will be taken up into the study protocol. The sponsor will inform the CA about the course of the investigation in security aspects according to the appropriate Directives and national legal requirements and also about the end and the results of the investigation.

13.4 Independent Ethics Committee

Prior to the start of the trial an application for the favorable opinion for Germany is submitted on behalf of the sponsor to the central independent, interdisciplinary ethics committee responsible under federal law for the principle investigator and to the local ethics committees responsible for the other participating institutions including a copy of the protocol, proposed informed consent form and other information and documents required by the ethics committees for their opinion. A copy of the written favorable opinion of the protocol and informed consent form must be available before the start of recruitment of subjects into the study. All changes of the study protocol or other study document classified “substantial” as well as adverse events, will be announced to the Independent Ethics Committee (IEC), according to the local requirements, e.g. for Germany §13, (2) und (3) GCP-V. Once a year or whenever it is questioned the IEC will get information about all SAR and about the security of the affected subjects, (e.g. according to §13. (6) GCP-V). Recommendations and tips of the IEC will be taken up into the study protocol. The sponsor will inform the IEC about the course of the Investigation in security aspects (e.g. according §13 GCP-V, (1) till (6)) and also about the end and the results of the investigation (e.g. according to §13 GCP-V, (8) and (9)).
The investigator cannot influence the decisions of the IEC. A list of the IEC members will be ordered.

13.5 Amendments

The appendices, attached to this protocol and referred to in the protocol, form an integral part of the protocol. No changes or amendments to this protocol may be made by the Investigator. The sponsor must submit and obtain favorable opinion/approval from the IEC and competent Higher Federal Authority for all subsequent protocol amendments. For changes to the informed consent form favorable opinion from the IEC might be necessary.

13.6 Study Reports

Within one year after the end of the trial a clinical trial report will be written and provided to the IEC and competent Higher Federal Authority independent of the completion or a premature closure of the trial.

13.7 Informed Consent

The informed consent form will be submitted together with the study protocol to the independent ethics committees (IEC) for review and approval. If requested, modifications must be incorporated. A copy of the written approval of the IEC must be available before starting the trial and dispensing any trial medication to trial subjects. The informed consent form must not be altered by the investigator except for contact data of the investigators. Changes to the informed consent form also have to be approved by the IEC. The revised form will be sent to all sites to replace the preceding version.
Before a subject’s participation in the clinical study, the investigator must obtain written informed consent from the subject. All subjects will be informed of the aims of the study, the possible adverse events, the anticipated benefits, the procedures and possible hazards to which he/she will be exposed, and the mechanism of treatment allocation the subjects also will be informed about alternative treatments. Subjects will be informed of their insurance protection and

the obligations which are linked to insurance. They will be informed as to the strict confidentiality of their subject data, but that their medical records may be reviewed for trial purposes by authorized individuals other than their treating physician. It will be emphasized that the participation is voluntary and that the subject is allowed to refuse further participation in the protocol whenever he/she wants. This will not prejudice the subject's subsequent care. The informed consent procedure must conform to the ICH guidelines on Good Clinical Practice.
The informed consent consists of three parts: consent to the diagnostic and therapeutic procedures of the trial, consent to the collection and storage of biological material, and consent to the processing and storage of data. The latter one includes consent to inspections where records may be reviewed by authorized individuals (other than their treating physician) of the sponsor or surveillance authorities / ethics committees. If the subject does not consent to the collection, processing and storage of his data, inclusion in the study is not possible and the subject's refusal should be documented in the medical notes.
The subject must be informed about the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any study treatment are administered. The collection and storage of biological material in this clinical trial is optional; consent to this part of the trial is not necessary for the participation in this clinical trial.
The investigator is also responsible for asking the subject if the subject agrees to have his/her primary care physician informed of the subject's participation in the clinical study. If the subject agrees to such notification, the investigator shall inform the subject's primary care physician of the subject's participation in the clinical study.
If a potential subject is illiterate or visually impaired, the investigator must provide an impartial witness to read the informed consent form to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the informed consent form to attest that informed consent was freely given and understood.
Adequate explanations of the aims, methods, anticipated benefits, and potential hazards of the study, the mechanism of treatment allocation must be given. The subject will have enough time to decide to participate in the study or not.
The acquisition of informed consent and the subject's agreement or refusal of his/her notification of the primary care physician must be documented in the subject's medical records, and the informed consent form must be signed and personally dated by the subject and by the investigator. One signed original of the informed consent form must be retained in accordance with institutional policy and another original must be provided to the subject. Treatment cannot start before the subject has signed the informed consent, meets all inclusion and no exclusion criteria and is registered.
With signing the informed consent form the investigator confirms that an individual clarification conversation has taken place and that the subject has signed the informed consent form.

13.8 Subject Confidentiality

The investigator must ensure that the subject's confidentiality is maintained. On the case report forms, subjects should be identified by their subject study number and only on the SAE report form additionally the age.
In compliance with ICH-GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the sponsor, and of regulatory

agencies direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform and obtain the consent of the subject to permit named representatives to have access to his/her study-related records without violating the confidentiality of the subject. The investigator must keep a list for the identification of the subjects (including name, birthday, gender, date of informed consent, date of randomization / registration).

13.9 Study Documentation and Archive

The investigator must maintain a list of appropriately qualified persons to whom he/she has delegated study duties, including all those authorized to make entries and/or corrections on case report forms.
Source documents are original documents, data, and records from which the subject's case report form data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.
The investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives from the study sponsor and/or applicable regulatory authorities. Elements include:

- Subject files containing completed case report forms, informed consent forms, and subject identification list.
- Study files containing the protocol with all amendments, the summary of product characteristics, copies of pre-study documentation, and all correspondence to and from the IEC.
- If kept, proof of receipt, Investigational Product Accountability Record, Return of Investigational Product for Destruction, Final Investigational Product Reconciliation Statement, and all drug-related correspondence.

In addition, all original source documents supporting entries in the case report forms must be maintained and be readily available.
All study documents and source documents must be kept for at least 10 years from submission of the final study report. Should the investigator wish to assign the study records to another party or move them to another location, he/she must notify the sponsor in writing of the new responsible person and/or the new location.

13.10 Compensation

Subjects will not be paid for participating in this clinical trial.

14. Trial Sponsorship and Financing

The AIO-Studien-gGmbH is the legal sponsor of the trial and finances the trial. Financial and material support for the conduction of the trial is granted by Bristol-Myers Squibb.

15. Trial Insurance

For all subjects participating in the trial the sponsor has taken out a liability insurance policy (mentioned below) according to the respective national law (e.g. § 40 (1) Nr. 8 und (3) German drug law (AMG)) which covers the sponsor, the

investigator and his co-workers against liability in the event that a subject's health is injured during the course of the clinical trial. The insurance policy provides benefits, even when no one else is liable for the damage death of or injury to any subject during the trial.

A certificate of insurance and conditions will be provided to the investigators and the subjects.

16. Trial Registration

The trial is registered at Clinical Trials Gov start of the study (FPI).

17. Publication Policy

After receiving the biometrical results a final report will be published and further publications (abstracts etc.) will be done. First author of the final publication will be the principal investigator of the study. All participating sites recruiting at least 10% of the patients will become a co-authorship if possible according to the publication policy of the journal. Persons involved in planning, conducting and evaluating the trial will be offered co-authorships. All co-authors will get the option to comment on the manuscript before publication.

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Appendix B: Performance status scale

STATUS	SCALES		STATUS
	KARNOFSKY	ECOG-WHO	
Normal, no complaints	100	0	Normal activity
Able to carry on normal activities Minor signs or symptoms of disease	90	0	Symptoms, but fully ambulatory
Normal activity with effort	80	1	
Cares for self. Unable to carry on normal activity or to do active work	70	1	Symptomatic, but in bed < 50% of the day.
Requires occasional assistance, but able to care for most of his needs	60	2	
Requires considerable assistance and frequent medical care	50	2	Needs to be in bed> 50% of the day, but not bedridden
Disabled. Requires special care and assistance	40	3	
Severely disabled. Hospitalization indicated though death non imminent	30	3	Unable to get out of bed
Very sick. Hospitalization necessary. Active supportive treatment necessary	20	4	
Moribund	10	4	
Dead	0	5	Dead

Appendix C: Common Terminology Criteria for Adverse Events (CTCAE)

In the present study, adverse events and/or adverse drug reactions will be recorded according to the

Common Terminology Criteria for Adverse Events (CTCAE), version 4.03.

At the time this protocol was issued, the full CTC document was available on the NCI web site, at the following address: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

Another option is via the EORTC Headquarters web site www.eortc.be, which provides a link to the appropriate CTC web site. This link will be updated if the CTC address is changed.

Appendix D: Modified Response Evaluation Criteria in Solid Tumors

Conventional response criteria may not be adequate to characterize the anti-tumor activity of immunotherapeutic agents like nivolumab and ipilimumab, which can produce delayed responses that may be preceded by initial apparent radiological progression, including the appearance of new lesions. Therefore, modified response criteria have been developed that account for the possible appearance of new lesions and allow radiological progression to be confirmed at a subsequent assessment. In this protocol, patients will be permitted to continue study treatment even after modified Response Evaluation Criteria in Solid Tumors (RECIST) criteria for progressive disease are met if the risk/benefit ratio is judged to be favorable.
Modified RECIST is derived from RECIST, Version 1.1 conventions (Eisenhauer, Therasse et al. 2009) and immune-related response criteria (irRC) (Wolchok, Hoos et al. 2009). *When not otherwise specified, RECIST v1.1 conventions will apply.*

Modified RECIST and RECIST, Version 1.1: Summary of Changes

	RECIST v1.1	Modified RECIST
New lesions after baseline	Define progression.	New measurable lesions are added into the total tumor burden and followed.
Non-target lesions	May contribute to the designation of overall progression	Contribute only in the assessment of a complete response
Radiographic progression	First instance of > 20% increase in the sum of diameters or unequivocal progression in non-target disease	Determined only on the basis of measurable disease; *must* be confirmed by a consecutive assessment > 4 weeks from the date first documented

RECIST = Response Evaluation Criteria in Solid Tumors.

DEFINITIONS OF MEASURABLE/NON-MEASURABLE LESIONS

All measurable and non-measurable lesions should be assessed at screening and at the protocol-specified tumor assessment timepoints. Additional assessments may be performed, as clinically indicated for suspicion of progression. The investigator will evaluate response to treatment using modified RECIST.

MEASURABLE LESIONS

Tumor Lesions. Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size as follows:
10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval no greater than 5 mm)
10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)

Malignant Lymph Nodes. To be considered pathologically enlarged and measurable, a lymph node must be >15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and follow-up, only the short axis will be measured and followed.

NON-MEASURABLE LESIONS

Non-measurable tumor lesions encompass small lesions (longest diameter < 10 mm or pathological lymph nodes with short axis > 10 but < 15 mm), as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, and abdominal mass/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

SPECIAL CONSIDERATIONS REGARDING LESION MEASURABILITY

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment, as outlined below.

BONE LESIONS

Bone scan, positron emission tomography (PET) scan, or plain films are not considered adequate imaging techniques for measuring bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions. Lytic bone lesions or mixed lytic–blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above. Blastic bone lesions are non-measurable.

CYSTIC LESIONS

Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

TUMOR RESPONSE EVALUATION

DEFINITIONS OF TARGET/NON-TARGET LESIONS

Target Lesions

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means that, for instances in which patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be recorded as non-measurable lesions (even if the size is < 10 mm by CT scan).

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs, but in addition, should lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance, the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of > 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT, this is almost always the axial plane; for MRI, the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal

node that is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis > 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis of < 10 mm are considered non-pathological and should not be recorded or followed. Lesions irradiated within 3 weeks prior to Cycle 1, Day 1 may not be counted as target lesions.

Non-Target Lesions

All other lesions (or sites of disease), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required.

It is possible to record multiple non-target lesions involving the same organ as a single item on the Case Report Form (CRF) (e.g., “multiple enlarged pelvic lymph nodes” or “multiple liver metastases”).

After baseline, changes in non-target lesions will contribute only in the assessment of complete response (i.e., a complete response is attained only with the complete disappearance of all tumor lesions, including non-target lesions) and will not be used to assess progressive disease.

New Lesions

During the study, all new lesions identified and recorded after baseline must be assessed at all tumor assessment timepoints. New lesions will also be evaluated for measurability with use of the same criteria applied to prospective target lesions at baseline per RECIST, (e.g., non-lymph node lesions must be < 10mm; see note for new lymph node lesions below). Up to a maximum of five new lesions total (and a maximum of two lesions per organ), all with measurements at all timepoints, can be included in the tumor response evaluation. New lesion types that would not qualify as target lesions per RECIST cannot be included in the tumor response evaluation.

New lesions that are not measurable at first appearance but meet measurability criteria at a subsequent timepoint will be measured from that point on and contribute to the sum of longest diameters (SLD), if the maximum number of 5 measurable new lesions being followed has not been reached.

CALCULATION OF SUM OF THE DIAMETERS

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated as a measure of tumor burden.

The sum of the diameters is calculated at baseline and at each tumor assessment for the purpose of classification of tumor responses.

Sum of the Diameters at Baseline: The sum of the diameters for all target lesions identified at baseline prior to treatment on Day 1.

Sum of the Diameters at Tumor Assessment: For every on-study tumor assessment collected per protocol or as clinically indicated, the sum of the diameters at tumor assessment will be calculated using tumor imaging scans. All target lesions and all new measurable lesions that have emerged after baseline will contribute to the sum of the diameters at tumor assessment. Hence, each net percentage change in tumor burden per assessment with use of modified RECIST accounts for the size and growth kinetics of both old and new lesions as they appear.

Note: In the case of new lymph nodes, RECIST v1.1 criteria for measurability (equivalent to baseline target lesion selection) will be followed. That is, if at first appearance the short axis of a new lymph node lesion > 15 mm, it will be considered a measureable new lesion and will be tracked and included in the SLD. Thereafter, the lymph node lesion will be measured at subsequent timepoints and measurements will be included in the SLD, even if the short axis diameter decreases to< 15 mm (or even < 10 mm). However, if it subsequently decreases to < 10 mm, and all other lesions are no longer detectable (or

have also decreased to a short axis diameter of < 10 mm if lymph nodes), then a response assessment of CR may be assigned.
If at first appearance the short axis of a new lymph node is > 10 mm and < 15 mm, the lymph node will not be considered measurable but will still be considered a new lesion. It will not be included in the SLD unless it subsequently becomes measurable (short axis diameter > 15 mm).
The appearance of new lymph nodes with diameter < 10 mm should not be considered pathological and not considered a new lesion.

RESPONSE CRITERIA

Evaluation of Target Lesions
Complete Response (CR): Disappearance of all target lesions. Lymph nodes that shrink to < 10 mm short axis are considered normal.
Partial Response (PR): At least a 30% decrease in the sum of the diameters of all target and all new measurable lesions, taking as reference the baseline sum of diameters, in the absence of CR.
Note: The appearance of new measurable lesions is factored into the overall tumor burden but does not automatically qualify as progressive disease until the sum of the diameters increases by > 20% when compared with the sum of the diameters at nadir.
Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of the diameters while on study.
Progressive Disease (PD): At least a 20% increase in the sum of diameters of all target and all new measurable lesions, taking as reference the smallest sum on study (nadir SID; this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

Impact of New Lesions on Modified RECIST
New lesions alone do not qualify as progressive disease. However, their contribution to total tumor burden is included in the sum of the diameters, which is used to determine the overall modified RECIST tumor response.

EVALUATION OF BEST OVERALL RESPONSE USING MODIFIED RECIST

TIMEPOINT RESPONSE
It is assumed that at each protocol-specified timepoint, a response assessment occurs. Table 1 provides a summary of the overall response status calculation at each timepoint for patients who have measurable disease at baseline.

MISSING ASSESSMENTS AND *NOT EVALUABLE* DESIGNATION
When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable (NE) at that timepoint. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and at follow-up only two lesions were assessed but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

Table 1 Modified RECIST Timepoint Response Definitions

% Change in Sum of the Diameters (Including Measurable New Lesions When Present)	Target Lesion Definition	Non-Target Lesion Definition	New Measurable Lesions	New Unmeasurable Lesions	Overall Modified RECIST Timepoint Response
- 100% [a]	CR	CR	No	No	CR
- 100% [a]	CR	Non-CR or not all evaluated	No	No	PR
≤ - 30%	PR	Any	Yes or no	Yes or no	PR
> - 30% to < + 20%	SD	Any	Yes or no	Yes or no	SD
Not all evaluated	Not evaluated	Any	Yes or no	Yes or no	NE
≥ + 20%	PD	Any	Yes or no	Yes or no	PD

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease.

[a] When lymph nodes are included as target lesions, the % change in the sum of the diameters may not be 100% even if complete response criteria are met since a normal lymph node is defined as having a short axis of < 10 mm. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm in order to meet the definition of CR.

BEST OVERALL RESPONSE: ALL TIMEPOINTS

The best overall response is determined once all the data for the patient are known. The best overall response according to modified RECIST is interpreted as below:

CR: Complete disappearance of all tumor lesions (target and non-target) and no new measurable or unmeasurable lesions, confirmed by a consecutive assessment > 4 weeks from the date first documented. All lymph nodes short axes must be < 10 mm.

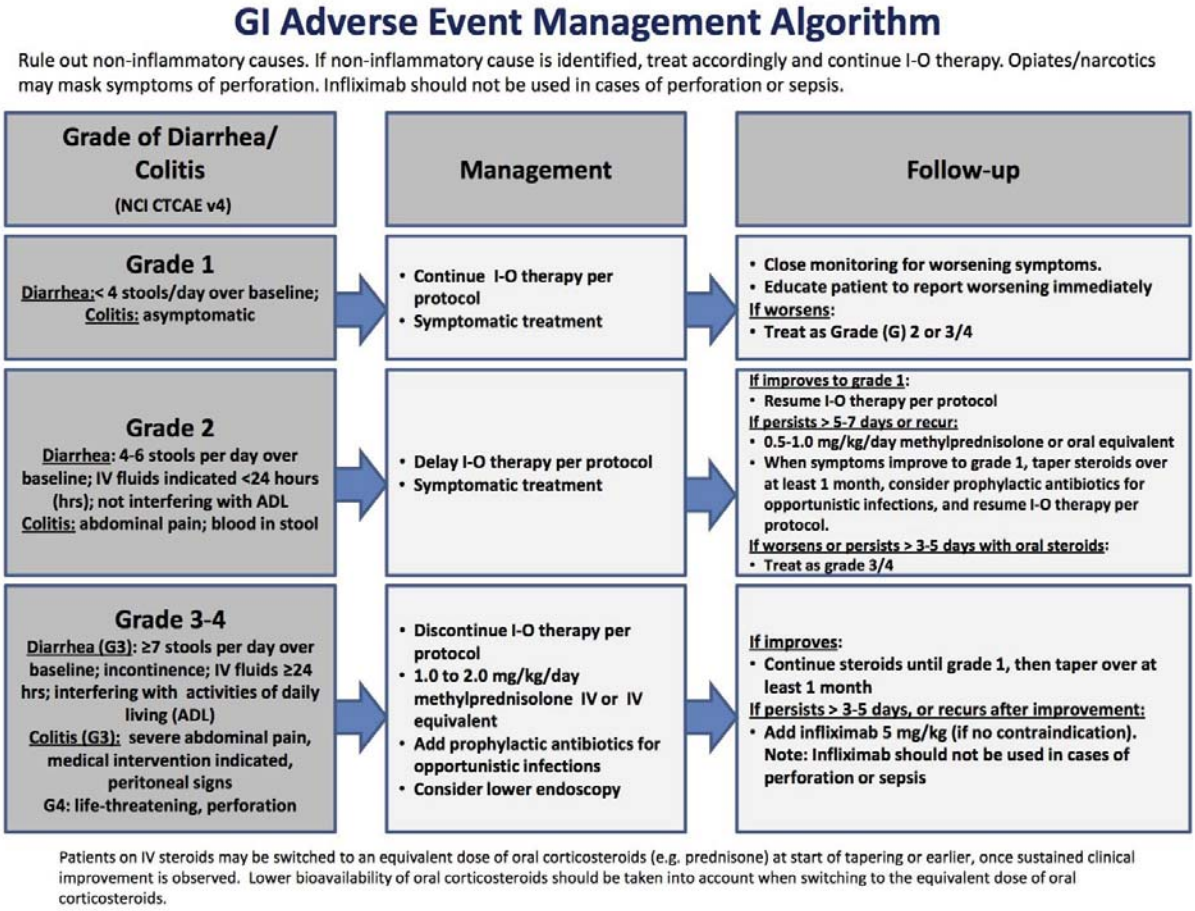
PR: Decrease in the sum of the diameters of all target and all new measurable lesions ≥ 30% relative to baseline, in the absence of CR, confirmed by a consecutive assessment > 4 weeks from the date first documented.

SD: Criteria for CR, PR, and PD are not met.

PD: Increase in the sum of the diameters of all target and all new measurable lesions ≥ 20% relative to the nadir, which *must* be confirmed by a consecutive assessment > 4 weeks from the date first documented as follows:

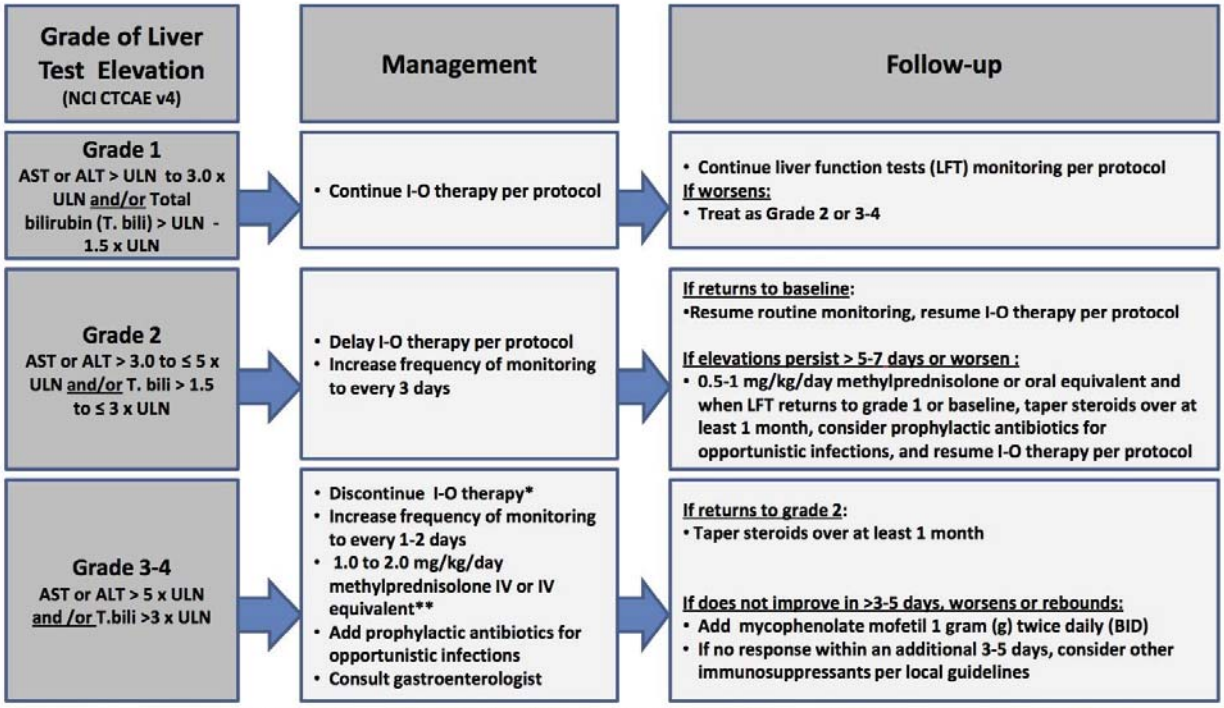
The confirmatory assessment shows an additional measurable increase in tumor burden as measured by the sum of the diameters of all target and all new measurable lesions.

Appendix E: Algorithm for toxicity management



Hepatic Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider imaging for obstruction.



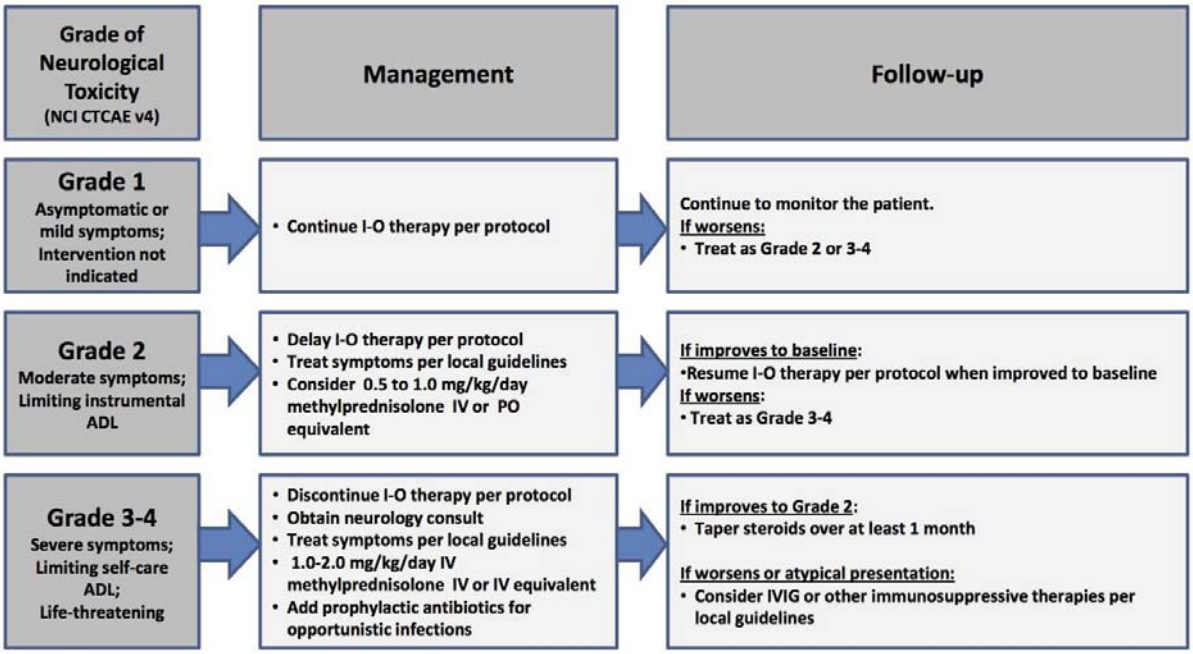
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

***I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN and T.bili ≤ 5 x ULN.**

**The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

Neurological Adverse Event Management Algorithm

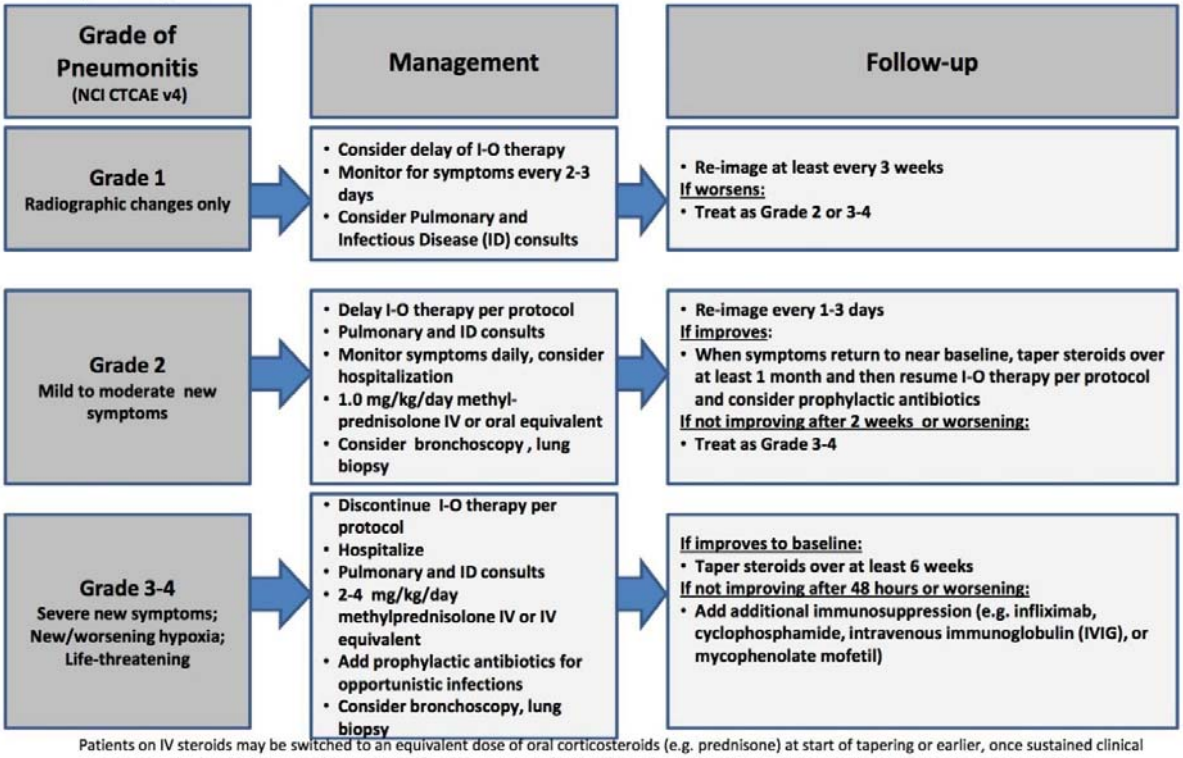
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Pulmonary Adverse Event Management Algorithm

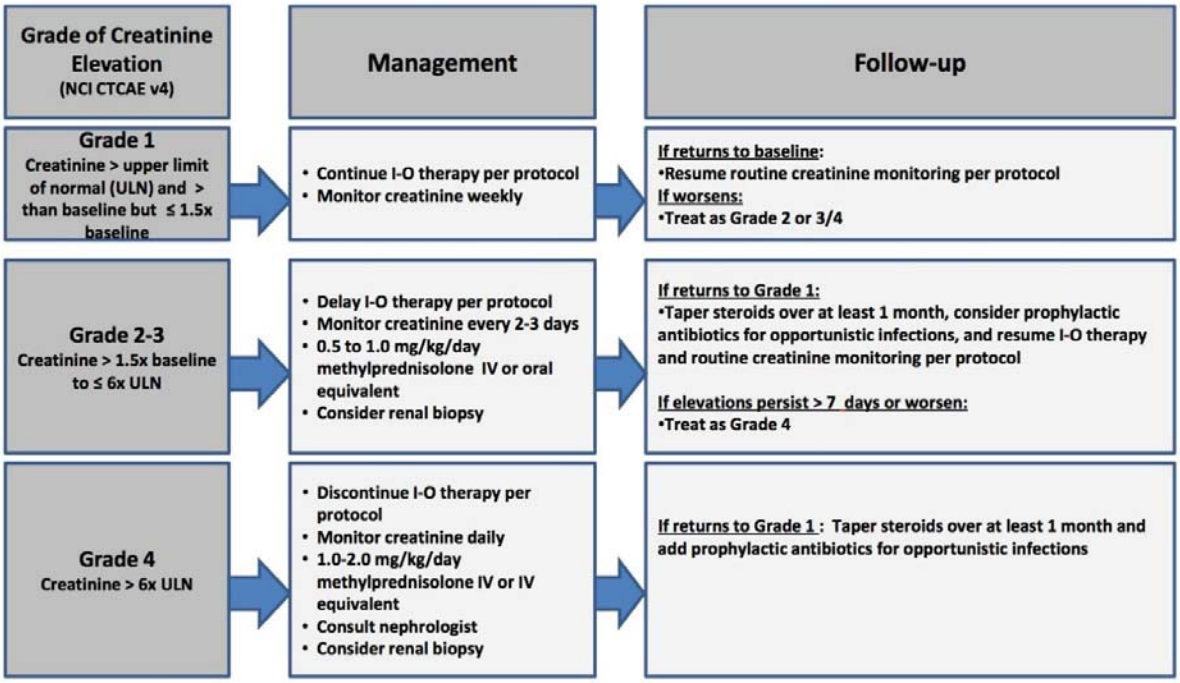
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Renal Adverse Event Management Algorithm

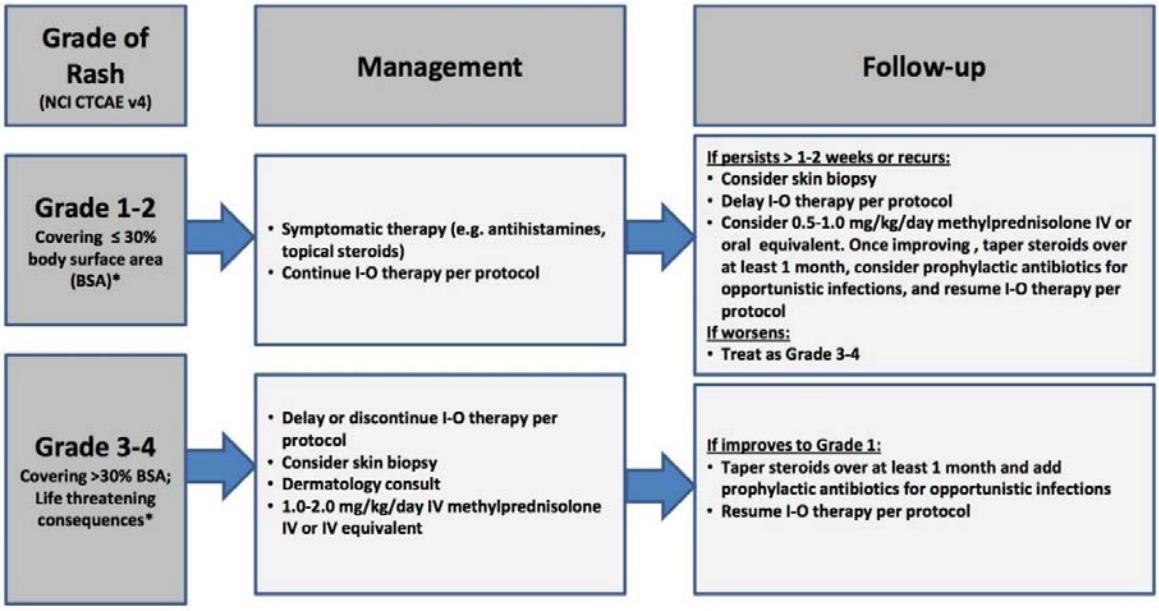
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Skin Adverse Event Management Algorithm

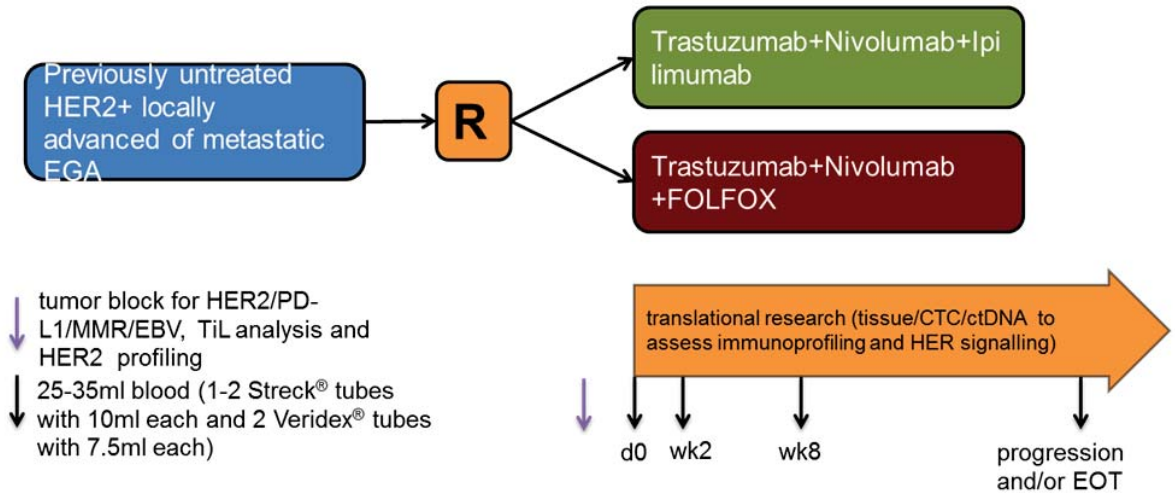
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
*Refer to NCI CTCAE v4 for term-specific grading criteria.

Appendix F: Translational research working instructions

Contact/Questions: intega@uke.de



Overview of translational research

Blood draw

- **Acquisition of blood in Streck® and Veridex® tubes**
  - Timepoints: prior to treatment (d0), day 1 cycle 2 (wk2) and cycle 5 (wk8), and at progression and/or end of treatment (25-35ml)
  - Blood will be collected in 2 (baseline) or 1 (all other timepoints) Streck® tubes (10ml each) and 2 Veridex® tubes (7.5ml each) and immediately shipped using the prelabbeled envelopes to

    Binder Laboratories
    Martinistrasse 52
    Hamburg 20246

Lab kits, including the Streck® and Veridex® tubes, labels and working instructions will be provided.

Tissue

Obtain paraffin embedded tissue. Preferably the tumor block or alternatively up to 10 unstained slides. The tissue will be immediately shipped using the prelabbeled envelopes to

Binder Laboratories
Martinistrasse 52
Hamburg 20246

Appendix G: MDRD formula

Formula:

GFR (ml/min/1,73m^2) = 186 x Serum-Creatinine $^{-1,154}$ x age $^{-0,203}$ [x 0,742 only in women] [x 1,21 in patients with black skin color]

Correction on body surface area: divide GFR by body surface area from nomogram