KURZPROTOKOLL
JAVELIN

Öffentlicher Titel	Phase III Studie zu Avelumab als Drittlinienbehandlung von metastasiertem oder lokal fortgeschrittenem, nicht resektablem Karzinom des Magens und des Gastroösophagalen Übergangs
Wissenschaftl. Titel	A Phase III open-label, multicenter trial of avelumab (MSB0010718C) as a third-line treatment of unresectable, recurrent, or metastatic gastric or gastroesophageal junction adenocarcinoma
Kurztitel	JAVELIN
Studienart	multizentrisch, prospektiv, Therapiestudie, randomisiert, offen/unverblindet, zweiarmig
Studienphase	Phase III
Erkrankung	Verdauung: Magen-/Speiseröhrenkrebs (Magen-/Ösophaguskarzinom): Zweitlinie oder höher
Einschlusskriterien	- Signed written informed consent before any trial-related procedure is undertaken that is not part of the standard patient management - Male or female subjects aged >= 18 years - Availability of a formalin-fixed, paraffin-embedded (FFPE) block containing tumor tissue or a minimum of 7 slides (preferably 10) unstained tumor slides suitable for PD -L1 expression assessment. PD-L1 expression determination is not a requirement for enrollment and will be done retrospectively - Subjects with histologically confirmed unresectable, recurrent, locally advanced or metastatic adenocarcinoma of the stomach or the gastroesophageal junction - Documented objective radiographic or clinical disease progression (e.g., any new or worsening malignant effusion documented by ultrasound examination) that may be confirmed by pathologic criteria (histology and/or cytology). - Subjects must have received 2 prior courses of systemic treatment for unresectable, recurrent, locally advanced or metastatic gastric cancer, and must have progressed after the second line. a. Acceptable regimens as first-line treatment of unresectable, recurrent, locally advanced or metastatic gastric cancer may include the following: i. Fluoropyrimidine-platinum-based double 1. Fluoropyrimidine components can consist of S1, 5-fluorouracil, or capecitabine 2. Platinum component can consist of either oxaliplatin or cisplatin ii. Fluoropyrimidine-platinum-based triplets consisting of the addition of docetaxel or epirubicin to a fluoropyrimidine-platinum-based doublet iii. FOLFIRI, which consists of the administration of fluorouracil, leucovorin, and irinotecan iv. Any prior adjuvant or neo-adjuvant treatment is allowed. Treatment with adjuvant or neo-adjuvant fluoropyrimidine-platinum-containing doublets will be considered as a first-line if relapse occurs within 6 months after the last administration of the platinum salt. b. Second-line therapy is defined as any of the following: i. Another line of a platinum doublet or FOLFIRI if the disease has progressed more than 6 months after completion of the first-line combination therapy ii. Ramucirumab (as a single agent or in combination) iii. Docetaxel (as a single agent or in combination) iv. Paclitaxel (as a single agent or in combination) (nab-paclitaxel is acceptable) v. Irinotecan (as a single agent or in combination) Trastuzumab in combination with first-line therapy or second-line therapy listed above for HER2 – neu overexpressing adenocarcinoma is acceptable. - ECOG PS of 0 to 1 at trial entry - Adequate hematological function defined by white blood cell count >= 2.0 × 109/L with absolute neutrophil count >= 1.0 × 109/L, lymphocyte count >= 0.5 × 109/L, platelet count >= 100 × 109/L, and hemoglobin >= 9 g/dL (may have been transfused) - Adequate hepatic function defined by a total bilirubin level <= 1.5 × the upper limit of normal (ULN) and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels <= 2.5 × ULN for all subjects

- Negative blood pregnancy test at screening for women of childbearing potential. For the purposes of this trial, women of childbearing potential are defined as: “All female subjects after puberty unless they are post-menopausal (age-related amenorrhea >= 12 consecutive months and increased follicle-stimulating hormone [FSH] > 40 mIU/mL), are surgically sterile, or are sexually inactive”.
- Highly effective contraception (i.e. methods with a failure rate of less than 1% per year) for both male and female subjects if the risk of conception exists (Note: The effects of the trial treatment on the developing human fetus are unknown; thus, women of childbearing potential and men must agree to use highly effective contraception, defined in Appendix II or as stipulated in national or local guidelines. Highly effective contraception must be used 15 days prior to first trial treatment administration and for the duration of trial treatment for all subjects. Highly effective contraception must be used at least for 60 days after stopping avelumab treatment and as indicated in the respective label (SmPC) for irinotecan or paclitaxel for subjects receiving chemotherapy or as per label of any other therapy used as BSC. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this trial, the treating physician should be informed immediately).

Ausschlusskriterien

- Prior therapy with any antibody or drug targeting T-cell coregulatory proteins (immune checkpoints), such as PD-1, PD-L1, or cytotoxic T-lymphocyte antigen-4. Adjuvant therapy is acceptable as described in Section 5.3.1. Maintenance treatment with oral fluoropyrimidine is acceptable.
- Concurrent anticancer treatment (for example, cytoreductive therapy, radiotherapy [with the exception of palliative bone-directed radiotherapy], immune therapy, or cytokine therapy, except for erythropoietin)
- Major surgery for any reason, except diagnostic biopsy, within 4 weeks of the trial treatment and/or if the subject has not fully recovered from the surgery within 4 weeks of the trial treatment
- Subjects receiving immunosuppressive agents (such as steroids) for any reason should be tapered off these drugs before initiation of the trial treatment (with the exception of subjects with adrenal insufficiency, who may continue corticosteroids at physiologic replacement dose, equivalent to < 10 mg prednisone daily). Note: a. Subjects receiving bisphosphonate or denosumab are eligible provided treatment was initiated at least 14 days before first dose of trial treatment; b. Previous or ongoing administration of systemic steroids for the management of an acute allergic phenomenon is acceptable as long as it is anticipated that the administration of steroids will be completed in 14 days, or that the daily dose after 14 days will be <= 10 mg per day of equivalent prednisone
- All subjects with brain metastases, except those meeting the following criteria: a. Brain metastases have been treated locally, have not been progressing at least 2 months after completion of therapy, and no steroid maintenance therapy is required, and b. No ongoing neurological symptoms that are related to the brain localization of the disease (sequelae that are a consequence of the treatment of the brain metastases are acceptable)
- Previous malignant disease (other than gastric cancer) within the last 5 years with the exception of basal or squamous cell carcinoma of the skin or carcinoma in situ (bladder, cervical, colorectal, breast)
- Prior organ transplantation, including allogeneic stem cell transplantation

- Significant acute or chronic infections, including, among others: a. Known history of testing positive for human immunodeficiency virus or known acquired immunodeficiency syndrome; b. Positive test for hepatitis B virus surface antigen and/or confirmatory hepatitis C virus ribonucleic acid (if anti-hepatitis C virus antibody tested positive); c. Active tuberculosis (history of exposure or history of positive tuberculosis test; plus presence of clinical symptoms, physical or radiographic findings)
- Active autoimmune disease that might deteriorate when receiving an immunostimulatory agent: a. Subjects with diabetes type I, vitiligo, psoriasis, hypo- or hyperthyroid disease not requiring immunosuppressive treatment are eligible; b. Subjects requiring hormone replacement with corticosteroids are eligible if the steroids are administered only for the purpose of hormonal replacement and at doses <= 10 mg or 10 mg equivalent prednisone per day; c. Administration of steroids through a route known to result in a minimal systemic exposure (topical, intranasal, intro-ocular, or inhalation) are acceptable
- Known severe hypersensitivity reactions to monoclonal antibodies (Grade >= 3 NCI-CTCAE v4.03), any history of anaphylaxis, or uncontrolled asthma (that is, 3 or more features of partially controlled asthma)
- Persisting toxicity related to prior therapy of Grade >= 2 NCI-CTCAE v4.03 (except neuropathy [see exclusion criterion #12] and alopecia)
- Neuropathy >= Grade 3
- Pregnancy or lactation
- Known alcohol or drug abuse
- History of uncontrolled intercurrent illness including but not limited to: a. Hypertension uncontrolled by standard therapies (not stabilized to 150/90 mmHg or lower); b. or, uncontrolled active infection;c. or, uncontrolled diabetes (e.g., hemoglobin A1c >= 8%)
- Clinically significant (that is, active) cardiovascular disease: cerebral vascular accident/stroke (< 6 months prior to enrollment), myocardial infarction (< 6 months prior to enrollment), unstable angina pectoris, congestive heart failure (New York Heart Association Classification Class II), or serious cardiac arrhythmia requiring medication (including corrected QT interval [QTc] prolongation of > 470 msec calculated according to Fridericia and/or pacemaker or prior diagnosis of congenital long QT syndrome)
- All other significant diseases (for example, inflammatory bowel disease), which, in the opinion of the Investigator, might impair the subject’s tolerance of trial treatment
- Any psychiatric condition that would prohibit the understanding or rendering of informed consent and that would limit compliance with trial requirements
- Vaccination within 4 weeks of the first dose of avelumab and while on trial is prohibited except for administration of inactivated vaccines (for example, inactivated influenza vaccines)
- Legal incapacity or limited legal capacity
- Subjects will be excluded from the treatment with irinotecan or paclitaxel monotherapy if administration of their chemotherapy would be inconsistent with the current local labeling (e.g., in regard to contraindications, warnings/precautions, or special provisions) for that chemotherapy. Investigators should check updated labeling via relevant websites before randomization

Alter 18 Jahre und älter

Fallzahl 330

KURZPROTOKOLL
JAVELIN

Prüfzentren	**Krankenhaus Nordwest GmbH** (Rekrutierung beendet) Institut für klinisch-onkologische Forschung Steinbacher Hohl 2-26 60488 Frankfurt am Main Prof. Dr. med. Salah-Eddin Al-Batran Tel: 069 7601 4420 albatran.salah@khnw.de
Sponsor	EMD Serono (Hauptsponsor) Merck Serono
Registrierung in anderen Studienregistern	ClinicalTrials.gov NCT02625623 EudraCT 2015-003301-42