KURZPROTOKOLL
Intega

Öffentlicher Titel	Phase II Studie zu Ipilimumab bei neu diagnostiziertem, HER2+ Adenokarzinom des gastroösophagealen Übergangs
Wissenschaftl. Titel	Ipilimumab oder FOLFOX in Kombination mit Nivolumab und Trastuzumab bei unbehandelten HER2 positiven lokal fortgeschrittenem oder metastasiertem Gastroösophagealem Adenokarzinom
Kurztitel	Intega
Studienart	multizentrisch, prospektiv, Therapiestudie, randomisiert, offen/unverblindet, zweiarmig, Investigator Initiated Trial (IIT)
Studienphase	Phase II
Erkrankung	Verdauung: Magen-/Speiseröhrenkrebs (Magen-/Ösophaguskarzinom): Erstlinie
Einschlusskriterien	- 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 - 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)) - Subject must be previously untreated with systemic treatment (including HER 2 inhibitors) given as primary therapy for advanced or metastatic disease - 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 - Subjects must have measurable or evaluable non-measurable disease as assessed by the investigator, according to RECIST v1.1 (Appendix D) - ECOG performance status score of 0 or 1 (Appendix B) - Screening laboratory values must meet the following criteria (using NCI CTCAE v.4.03): - -> WBC >= 2000/MüL - -> 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 <= 5.0 X ULN if liver metastases 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) - Males and Females, >= 18 years of age - 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 - Subjects must be willing and able to comply with scheduled visits, treatment schedule, laboratory tests and other requirements of the study - 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

- 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
- 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

Ausschlusskriterien

- 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)
- 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
- History of exposure to the following cumulative doses of anthracyclines (epirubicin > 720 mg/m2, doxorubicin or liposomal doxorubicin > 360 mg/m2, mitoxantrone > 120 mg/m2 and idarubicin > 90 mg/m2, other (e.g., liposomal doxorubicin or other anthracycline greater than the equivalent of 360 mg/m2 of doxorubicin). If more than one anthracycline has been used, then the cumulative dose must not exceed the equivalent of 360 mg/m2 of doxorubicin
- Baseline LVEF value < 55%, assessed by echocardiogram [ECHO], multigated acquisition (MUGA) scan, or cardiac magnetic resonance imaging (MRI) scan
- 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
- 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
- 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
- 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

	- 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 - 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 - History of allergy or hypersensitivity to study drug or any constituent of the products - Participation in another clinical study with an investigational product during the last 30 days before inclusion - Patient who has been incarcerated or involuntarily institutionalized by court order or by the authorities § 40 Abs. 1 S. 3 Nr. 4 AMG - 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]
Alter	18 - 99 Jahre
Molekularer Marker	HER2/neu pos.
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