CHARITÉ

Comprehensive Cancer Center
Universitätstumorzentrum

Studientitel	**SUNIFORECAST** **A Phase 2, Randomized, Open-Label Study of Nivolumab Combined With Ipilimumab Versus Standard of Care in Subjects With Previously Untreated and Advanced (Unresectable or Metastatic) Non-clear Cell Renal Cell Carcinoma (nccRCC)**	
EudraCT-Nummer	**2016-000706-12**	
ClinicalTrials.gov Identifier	**NCT03075423**	
Sponsor	University of Frankfurt	
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Wichtigste Einschlusskriterien	1. Signed Written Informed Consent a) Subjects must have signed and dated an approved written informed consent form according to the Institutional Review Board (IRB) and 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. b) Subjects must be willing and able to comply with scheduled visits, treatment schedule, laboratory testing, and other requirements of the study. 2. Target Population a) Histological confirmation of non-clear cell renal cell carcinoma (nccRCC) with at least 50% non-clear cell component according to actual World Health Organization (WHO) classification. b) Advanced (not amenable to curative surgery or radiation therapy) or metastatic (AJCC Stage IV) nccRCC c) Performance status: Karnofsky (KPS) > 70% d) Measurable disease as per RECIST v 1.1 documented by an English radiology report e) Tumor tissue (FFPE archival or recent acquisition) must be available and sent to the central pathological reviewer (see Table 6) in order to confirm the diagnosis. (Note: Fine Needle Aspiration (FNA) and bone metastases samples are not acceptable for submission).	

	f) Patients with all risk categories will be eligible for the study. Patients will be stratified for papillary or non-papillary non-clear cell histology and IMDC risk score Patients will be categorized according to favorable versus intermediate versus poor risk status at registration according to the International Metastatic RCC Database Consortium (IMDC) criteria: i. KPS equal to 70% ii. < 1 year from diagnosis to randomization iii. Hemoglobin < than the lower limit of normal (LLN) iv. Corrected calcium concentration greater than the upper limit of normal (ULN) v. Absolute neutrophil count greater than the ULN vi. Platelet count greater than the ULN If none of the above factors are present, subjects are only eligible for the favorable-risk cohort, if 1-2 factors are present subjects are categorized as intermediate risk and > 3 factors as poor risk. 3. Age and Reproductive Status a) Males and Females, > 18 years of age b) 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. c) Women must not be breastfeeding d) WOCBP must agree to follow instructions for method(s) of contraception for a period of 30 days (duration of ovulatory cycle) plus the time required for the investigational drug to undergo five half-lives. The terminal half-lives of Nivolumab and Ipilimumab are up to 25 days and 18 days, respectively. The terminal half-life of the active metabolite of Sunitinib is up to 110 hours. The terminal half-life of other Standard of Care agents has to be derived from the product information. i. WOCBP randomized to receive Nivolumab + Ipilimumab should use an adequate method to avoid pregnancy for 23 weeks (30 days plus the time required for Nivolumab to undergo five half-lives) after the last dose of investigational drug. ii. WOCBP randomized to receive the Standard of Care agent should use an adequate method to avoid pregnancy for 8 weeks (30 days plus the time required for the active metabolite of the Standard of Care agent to undergo five half-lives) e) 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 five half-lives. The terminal half lives of Nivolumab and Ipilimumab are up to 25 days and 18 days, respectively. The terminal half-life of the active metabolite of Sunitinib is up to 110 hours.

	i. Males randomized to receive Nivolumab combined with Ipilimumab who are sexually active with WOCBP must continue contraception for 31 weeks (90 days plus the time required for Nivolumab to undergo five half-lives) after the last dose of investigational drug. ii. Males randomized to receive Sunitinib who are sexually active and women of childbearing potential (WOCBP) must continue contraception for 16 weeks (90 days plus the time required for the active metabolite of Sunitinib to undergo five half-lives) after the last dose of investigational drug. f) Azoospermic males and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However they must still 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 WOCBP and male subjects who are sexually active with WOCBP on the use of highly effective methods of contraception. Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly. At a minimum, subjects must agree to the use of two methods of contraception, with one method being highly effective and the other method being either highly effective or uncertain effective as listed below: HIGHLY EFFECTIVE METHODS OF CONTRACEPTION • Male condoms with spermicide • Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants and intrauterine devices (IUDs) by WOCBP subject or male subject's WOCBP partner • Female partners of male subjects participating in the study may use hormone based contraceptives as one of the acceptable methods of contraception since they will not be receiving study drug • Nonhormonal IUDs o Tubal ligation o Vasectomy o Complete Abstinence* ▪ Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable

	alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence. UNCERTAIN METHODS OF CONTRACEPTION • Diaphragm with spermicide • Cervical cap with spermicide • Vaginal sponge • Male Condom without spermicide • Progestin only pills by WOCBP subject or male subject's WOCBP partner • Female Condom*. o A male and female condom must not be used together