MASTERKEY-318

Trial to Evaluate the Safety of Talimogene Laherparepvec Injected Into Tumors Alone and in Combination With Systemic Pembrolizumab MK-3475-611/Keynote-611

NCT-Nummer:
NCT02509507

Studienbeginn:
Februar 2016

Letztes Update:
18.03.2021

Wirkstoff:
Talimogene Laherparepvec, Pembrolizumab
Indikation (Clinical Trials):
Carcinoma, Hepatocellular, Liver Neoplasms

Geschlecht:
Alle

Altersgruppe:
Erwachsene (18+)

Phase:
Phase 1

Sponsor:
Amgen

Collaborator:
Merck Sharp & Dohme Corp.

Studien-Informationen

Brief Summary:

This is a phase 1b/2, multicenter, open-label, basket trial to evaluate the safety of

talimogene laherparepvec injected intrahepatically into liver tumors alone and in combination

with systemic IV administration of pembrolizumab, in subjects with non-HCC liver metastases from BC, CRC, gastroesophageal cancer (GEC), melanoma, NSCLC, RCC in Part 1 Group A, and subjects with HCC with and without viral hepatitis in Part 1 Group B (viral hepatitis is only applicable in combination setting), and to evaluate the efficacy and safety of intratumoral talimogene laherparepvec in combination with systemic pembrolizumab in subjects with advanced

TNBC, hormone receptor positive breast cancer, CRC, CSCC, and BCC in Part 2 Group A and subjects with HCC with and without viral hepatitis in Part 2 Group B. The objective of Part 1 is to evaluate the safety of intrahepatic injection of talimogene laherparepvec into liver tumors alone and in combination with systemically administered pembrolizumab for the non-HCC (Group A) and HCC (Group B) cohorts separately. Part 2 consists of 2-stage design to evaluate the efficacy and safety of talimogene laherparepvec in combination with systemic pembrolizumab. Efficacy and safety will be evaluated in each of the five non-HCC tumor types from Group A separately. Similarly, the efficacy and safety of the combination treatment will be determined for Group B HCC subjects.

Ein-/Ausschlusskriterien

Summary of Subject Eligibility Criteria:

Key **Inclusion Criteria:**

Subjects must be age ≥ 18 years at the time of informed consent. Subjects must have histologically or cytologically confirmed disease.

Part 1 is restricted to BC, CRC, GEC, melanoma, NSCLC, or RCC with liver metastases or HCC.

Part 2 Group A is restricted to advanced hormone receptor positive BC, CRC, TNBC, CSCC, and BCC with or without liver metastases.

- Part 2 Hormone receptor positive Breast Cancer Arm only: Histologically and/or cytologically confirmed diagnosis of estrogen receptor (ER) positive and/or progesterone receptor (PrR) positive breast cancer.

- Triple negative breast cancer: Histologically and/or cytologically confirmed diagnosis of ER negative, PrR negative, human epidermal growth factor receptor 2 (HER2)-Neu negative.

Part 2 Group B is restricted to HCC (fibrolamellar and mixed hepatocellular/cholangiocarcinoma subtypes are not eligible).

For HCC subjects with a diagnosis of hepatitis B, they must be on antiviral therapy for at least 4 weeks prior to enrollment and HBV viral load by real-time polymerase chain reaction (qPCR) must be < 100 IU/mL. HCC subjects with past or ongoing hepatitis C infection must have completed treatment for hepatitis C at least 1 month prior to study enrollment and hepatitis C viral load must be undetectable; subjects with hepatitis B and C must fulfill the eligibility criteria for hepatitis B and hepatitis C. Subjects with unresectable locally recurrent TNBC are eligible.

Non-HCC subjects must have received at least 1 prior standard of care systemic anti-cancer therapy for their locally advanced or metastatic disease. For the combination cohorts (Cohorts 5 and 6 in Part 1) and Part 2, subjects with melanoma CSCC or NSCLC do not need to have received prior therapy. In Part 1, subjects must have measurable liver tumors and liver tumors that are suitable for injection. In Part 2, subjects must have measurable disease and cutaneous, subcutaneous, lymph node, or liver tumors suitable for injection.

Eastern Cooperative Oncology Group (ECOG) performance status must be 0 or 1, and life expectancy should be approximately 5 months or more. Adequate hematological, renal, hepatic, and coagulation function is required. Liver function tests may be mildly abnormal but within the parameters. Child-Pugh score must be A.

Key **Exclusion Criteria:**

Subjects must not be candidates for surgery or locoregional therapy with curative intent or planned systemic anti-cancer therapy, with the exception of immunotherapy in the combination cohorts (Cohorts 5 and 6 in Part 1 and all subjects in Part 2). Liver tumors must not be estimated to invade approximately more than one-third of the liver. Liver

tumor-directed therapy, hepatic surgery or major surgery, antibody-based therapy, or immunotherapy must not have been performed < 28 days, chemotherapy < 21 days, and targeted small molecule therapy or hormonal therapy < 14 days prior to enrollment. Subjects must either (1) have no central nervous system (CNS) metastasis, or carcinomatous meningitis, or (2) if CNS metastasis is present, must have stable treated cerebral metastases. Subjects must not have symptomatic auto-immune disease or be symptomatically immunosuppressed. They must not have a history of solid organ transplantation. For non-HCC, there must not be acute or chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infection. For HCC with prior hepatitis B and/or C infection, HBV and/or HCV viral load by qPCR must be undetectable, and they must not have had recent treatment within 12 weeks for HBV or HCV with certain antiviral medications in Part 1 Group B cohorts 1-5 and 6a, and Part 2 Group B HCC without viral hepatitis. For all patients in Part 1 and for patients in Part 2 where intrahepatic liver injection is planned, there should be no macroscopic intravascular invasion of tumors into the main portal vein, hepatic vein, or vena cava. Subjects must not: have active herpetic skin lesions or prior complications of herpetic infection (eg, herpetic keratitis or encephalitis); require treatment with an antiherpetic drug; have received live-virus vaccination within 30 days of planned treatment start; have previous therapy with talimogene laherparepvec, oncolytic viruses, or tumor vaccine. Subjects in the combination treatment cohort must not have: a history or evidence of psychiatric, substance abuse, or any other clinically significant disorder; toxic effects of the most recent prior chemotherapy not resolved to grade 1 or less (except alopecia); or expected other cancer therapy while on study with the exception of local radiation to the site of bone or other metastasis for palliative treatment. Male subjects of reproductive potential in the combination treatment must be willing to use acceptable methods of effective contraception during treatment and through 4 months after the last dose of pembrolizumab.

Studien-Rationale

Primary outcome:

1. Subject incidence DLTs separately in Group A and B observed in monotherapy and combination cohorts and in each tumor type seperately in Part 2 (Time Frame - 3 year)

2. To evaluate in Part 2 ORR per modified irRC-RECIST separately by tumor type (HR+, TNBC, CRC, BCC, CSCC, HCC) (Time Frame - 2 years)

Secondary outcome:

1. Safety: Subject incidence of treatment-related and treatment-emergent adverse events in monotherapy and combination of Part 1 and each separate tumour type in Part 2 (Time Frame - 5 years)

2. Safety: To estimate the incidence of detectable talimogene laherparepvec DNA in blood and urine (Time Frame - 5 years)

3. Safety: To estimate the incidence of clearance of talimogene laherparepvec DNA from blood and urine (Time Frame - 5 years)

4. Safety: To estimate the rate of detection and incidence of talimogene laherparepvec DNA and virus at the surface of talimogene laherparepvec injection site, the exterior of the occlusive dressing, and the oral mucosa (Time Frame - 5 years)

5. Safety: To estimate the incidence of talimogene laherparepvec DNA detection in lesions suspected to be herpetic in origin (Time Frame - 5 years)

6. Efficacy: Objective response rate (ORR) (Time Frame - 5 years):
To evaluate the efficacy of intrahepatic injection of talimogene laherparepvec in the overall population and by tumor type (non-hepatocellular carcinoma and hepatocellular carcinoma)

7. Efficacy: Best overall response (BOR) (Time Frame - 5 years):
To evaluate the efficacy of intrahepatic injection of talimogene laherparepvec in the overall population and by tumor type (non-hepatocellular carcinoma and hepatocellular carcinoma)

8. Efficacy: Durable response rate (DRR) (Time Frame - 5 years):
To evaluate the efficacy of intrahepatic injection of talimogene laherparepvec in the overall population and by tumor type (non-hepatocellular carcinoma and hepatocellular carcinoma)

9. Efficacy: Duration of response (DOR) (Time Frame - 5 years):
To evaluate the efficacy of intrahepatic injection of talimogene laherparepvec in the overall population and by tumor type (non-hepatocellular carcinoma and hepatocellular carcinoma)

10. Efficacy: Response in injected and uninjected lesions (Time Frame - 5 years):
To evaluate the efficacy of intrahepatic injection of talimogene laherparepvec in the overall population and by tumor type (non-hepatocellular carcinoma and hepatocellular carcinoma)

11. Efficacy: Disease control rate (DCR) (Time Frame - 5 years):
To evaluate the efficacy of intrahepatic injection of talimogene laherparepvec in the overall

population and by tumor type (non-hepatocellular carcinoma and hepatocellular carcinoma)

12. Efficacy Progression-free survival (PFS) (Time Frame - 5 years):
To evaluate the efficacy of intrahepatic injection of talimogene laherparepvec in the overall population and by tumor type (non-hepatocellular carcinoma and hepatocellular carcinoma)

13. Efficacy: Overall survival (OS) (Time Frame - 5 years):
To evaluate the efficacy of intrahepatic injection of talimogene laherparepvec in the overall population and by tumor type (non-hepatocellular carcinoma and hepatocellular carcinoma)

Studien-Arme

- Experimental: Phase Ib/II Talimogene Laherparepvec
  Talimogene Laherparepvec
- Experimental: Phase Ib/II Talimogene Laherparepvec + Pembrolizumab
  Combination treatment of Talimogene Laherparepvec and Pembrolizumab

Geprüfte Regime

- Talimogene Laherparepvec:
  Talimogene laherparepvec (T-VEC) administered by intralesional injection into liver tumors, with US/CT guidance. Part 1: initial dose of T-VEC is 10^6 PFU/mL up to 4mL in Cohorts 1 & 2, up to 8mL in Cohorts 3 & 4 of the Group A & Group B. The 1st cycle of T-VEC will be 21 (+3) days (from the 1st dose at 10^6 PFU/mL to the 2nd dose at 10^7 or 10^8 PFU/mL). Subsequent cycles of T-VEC will be 21 (±3) days. Max. volume of T-VEC administered at any dose is 4mL (Cohorts 1, 2, 5, and 6) or 8mL (Cohorts 3 & 4) for any individual lesion or for all lesions combined. Part 2: Initial dose of T-VEC is 10^6 PFU/mL followed by subsequent T-VEC doses at a concentration of 10^8 PFU/mL. T-VEC volume is up to 8mL based on the size of the inejected lesions.
- Pembrolizumab:
  Pembrolizumab is a non-Amgen Investigational product that is manufactured by Merck. Pembrolizumab will be labeled, packaged, and distributed by Amgen (or designee) using Amgen (or designee) clinical study drug distribution procedures. Pembrolizumab is supplied as pembrolizumab 100 mg/4 mL vials (25 mg/mL) solution for IV infusion. The trial treatment will consist of a total dose of 200mg administered intravenously every 3 weeks (day 1 of each cycle) for up to 35 cycles.

Studienleiter

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Quelle: ClinicalTrials.gov