P-54 Phase 2a study of NT-I7, a long-acting interleukin-7, plus pembrolizumab: Cohort of subjects with checkpoint inhibitor-naïve advanced MSS-colorectal cancer

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Background: Checkpoint inhibitor (CPI) monotherapy is ineffective for microsatellite stable colorectal cancer (MSS-CRC). NT-I7 (efineptakin alfa) is a long-acting IL-7 that can increase T-cell infiltration in the tumor microenvironment (TME). We hypothesize that NT-I7 may create a favorable immune-reactive TME to enhance the efficacy of CPI when combined with pembrolizumab (pembro).

Methods: This is an open-label, phase 2a study in subjects with relapsed/refractory (R/R) tumors, including CPI-naïve R/R MSS-CRC. Subjects were enrolled following Simon's 2-stage minimax design; 17 were enrolled in the first stage, and 8 additional subjects were enrolled for the second stage. Subjects received the recommended-phase-2-dose of NT-I7 intramuscularly at 1200 µg/kg every 6 weeks (Q6W) plus pembro 200 mg intravenously Q3W. Preliminary anti-tumor activity based on Overall Response Rate (ORR) was assessed by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and iRECIST. Biomarker analyses in peripheral blood and tumor biopsy were performed.

Results: As of 14-Jan-2022, 28 subjects were enrolled in the CPI-naïve R/R MSS-CRC cohort. Median age was 56.0 years [37-81], with ECOG PS 0 (28.6%) and 1 (71.4%). Twenty-three (82%) subjects received $\geq$ 2 prior therapies. All subjects had metastatic or locally advanced disease at enrollment. The median duration of follow-up was 5.3 months. Among these 25 evaluable subjects ORR and disease control rate (DCR) was 4% (1/25 subjects) and 40% (10/25) per RECIST v1.1; 12% (3/25 subjects) and 44% (11/25) per iRECIST. In addition to 3 subjects with iPR, 11 subjects are still ongoing to follow up responders. Interestingly, in patients with rectal malignancy both ORR and DCR by iRECIST were 50% (2/4). The ORR and DCR by iRECIST were 25% (1/4) and 50% (2/4) in 2L; 17% (1/6) and 33% (2/6) in 3L; and 13% (1/8) and 50% (4/8) in 4L. Among subjects without/with $\geq$ 2 liver mets, the ORR was 33.3% (2/6) vs 5.3% (1/19); DCR was 83.3% (5/6) vs 31.6% (6/19) and PFS was 11.6 weeks vs 6.1 weeks. All subjects with responses continue on treatment. Treatment-related adverse events (trAEs) occurred in 27 (96.4%) subjects, 12 (42.8%) G1-2 events and 14 (50%) G3 events; 1 (3.6%) G4 and no G5 trAEs were reported. No subjects discontinued from the study due to trAE. One iPR subject with available biopsy data showed an enhanced T-cell infiltration in the TME at week 5.

Conclusions: The chemotherapy-free combination of NT-I7 + pembro was well tolerated in heavily pretreated subjects with CPI-naïve R/R MSS-CRC. The encouraging antitumor activity showed that subjects without liver metastasis sites especially benefited from the combination of NT-I7 and pembro therapy. Biomarker analyses demonstrated improved peripheral and intratumoral T cell responses. Plan is to enroll 25 more patients to further evaluate efficacy of NT-I7 + pembro in CPI-naïve subjects with R/R MSS-CRC.

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P-55 Efficacy and safety data from patients with pre-treated metastatic colorectal cancer receiving trifluridine/tipiracil: Real-world data from the non-interventional TACTIC study

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Background: In the pivotal phase III RECOURSE trial, trifluridine/tipiracil (FTD/TPI) significantly improved overall and progression-free survival (OS, PFS) in patients with pre-treated metastatic colorectal cancer (mCRC) compared to placebo [1]. While randomised controlled trials represent the most reliable method of hypothesis testing, in- & exclusion criteria inevitably impede translation of their results to a real-world patient collective. Omitting restrictive in- & exclusion criteria we challenged the observations from the RECOURSE trial on a patient population which more accurately reflects daily clinical practice in Germany.

Methods: In this prospective, multi-centre, open-label, non-interventional study, patients with pre-treated mCRC were treated with oral FTD/TPI (35 mg/m2 bid on days 1 — 5 and 8 — 12 of each 28-day cycle). Primary endpoint was OS. Secondary endpoints included PFS and safety. Additionally, 3 subgroups were defined according to a post-hoc analysis of the RECOURSE trial [2]: best, good and poor prognostic characteristics (BPC, GPC, PPC). Patients with $<$ 3 metastatic sites at inclusion and $\geq$18 months from diagnosis to inclusion were considered to have GPC. GPC patients without liver metastasis at inclusion were considered to have BPC. All remaining patients were considered to have PPC.

Results: From June 2018 to August 2021, 307 patients were treated with FTD/TPI (mean treatment duration 3.4 cycles) at 52 German sites. Median age was 67.7 years and 17.0% of patients had an ECOG PS2/3. When focusing on patients with ECOG PS$\leq$1, median OS of patients in the full analysis set (n=243: 8.6 months; 95% CI 7.4 — 9.3) as well as of the defined subgroups (BPC n=54 vs GPC n=147 vs PPC n=96: 16.2 vs 9.8 vs 6.3 months; 95% CI 9.7 — 19.4 vs 8.6 — 11.7 vs 4.5 — 7.8) were in line with results of RECOURSE study (all patients n=534: 7.1 months/ BPC n=97 vs GPC n=261 vs PPC n=273: 16.4 vs 9.3 vs 5.3 months) [1] with a longer survival of patients with BPC and GPC compared to PPC. Similar results observed when analysing data from patients with ECOG PS$\leq$3 (all patients n=300: 7.4 months; 95% CI 6.4 — 8.6/ BPC n=65 vs GPC n=176 vs PPC n=124: 13.3 vs 8.9 vs 5.1 months; 95% CI 9.1 — 17.6 vs 7.6 — 9.8 vs 4.4 — 7.0). Median PFS of all patients in the full analysis set was 2.9 months (95% CI 2.8 — 3.3). BPC (n=65) and GPC (n=176) patients were characterised by a longer median PFS compared to PPC (n=124) patients (4.0 vs 3.4 vs 2.6 months; 95% CI 3.3 — 5.3 vs 3.0 — 3.7 vs 2.4 — 2.8). The most frequent TEAEs were anaemia (20.5%), leukopenia (18.6%) and neutropenia (16.9%).

Conclusions: Administration of FTD/TPI to patients with pre-treated mCRC was associated with prolonged survival, delayed progression and a manageable toxicity profile confirming efficacy and safety of FTD/TPI in a real-world population. Independent of other baseline characteristics such as ECOG PS and age, low metastatic burden and indolent disease were factors of good prognosis with regards of OS and PFS. [1]Mayer et al,NEnglJMed2015 [2]Tabernero et al,ESMOOpen2020.

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P-56 Estimating endpoint correlation between surrogate measures and overall survival using reconstructed survival data: Case studies from adjuvant and metastatic gastric cancer trials

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Background: Validation of intermediate endpoints such as disease-free survival (DFS) and progression-free survival (PFS) as surrogate predictors for overall survival (OS) in randomized controlled trials (RCTs) requires establishing their association at the individual-level. In the absence of individual-level patient data (IPD), this study developed an analytical framework to estimate this association between DFS/PFS and OS using reported Kaplan-Meier (KM) curves from the RCTs and demonstrated its predictive performance in adjuvant and metastatic gastric cancer (GC) treatment settings.

Methods: Assuming a three-state illness-death model for cancer survival, we developed a linear optimization model to elicit the underlying pre-progression death probability as well as post-progression survival (PPS) distribution using pseudo-patient level DFS/PFS and OS data reconstructed from the published KM curves. In the adjuvant setting, pre-progression death probability was bounded below by the cure rates which were estimated by fitting mixture cure models (MCMs) to the DFS data. In the MCMs, time-to-event outcomes for the uncured subpopulation were modeled using parametric survival functions suggested by National Institute for Health and Care Excellence (NICE) and non-disease-related mortality rates were derived from the age- and sex-adjusted local life-table data from World Health Organization. Reconstructed DFS/PFS distributions were extrapolated via parametric- and spline-based models suggested by NICE and adjusted with estimated background mortality rates whereas elicited PPS distributions were extrapolated assuming constant hazard rate over time. Estimated pre-progression death probabilities and modeled DFS/PFS/PPS distributions governed a Monte-Carlo simulation framework which generated paired pseudo pre- and post-progression data to predict Spearman's rank and Pearson's product moment correlation coefficients. Model performance was tested on two correlation meta-analyses in GC (14 RCTs with 3371 patients on adjuvant chemotherapy; 20 RCTs with 4069 patients on metastatic treatments) published in 2013 by the GASTRIC group. For each test case, model-predicted OS rates and Spearman rank correlation coefficients were compared against their reported counterparts and corresponding 95% CIs.

Results: Predicted OS curves laid within the 95% CIs of the reported OS KM-curves 96% and 100% of the time in the adjuvant and metastatic setting, respectively, where the average deviation between the restricted mean survival times under the model-predicted OS curves and the statistically best-fitting OS curves to the reported data was $<$ 1% in both settings. Average deviation between the estimated and reported Spearman rank correlation coefficients was no more than 0.01 (reported: 0.97 [95% CI:0.97-0.98] vs. predicted: 0.96 [95% CI:0.96-0.96]) and 0.13 (reported: 0.85 [95% CI:0.85-0.85] vs. predicted: 0.72 [95% CI:0.71-0.72]) in both settings. Predicted Pearson correlation coefficients were 0.95 [95% CI:0.95-0.95] and 0.94 [95% CI:0.94-0.95] in the adjuvant and metastatic setting, respectively.

Conclusions: Our study offers a useful approach for an indirect endpoint correlation assessment in the absence of IPD. Results indicate the model to be precise in adjuvant but conservative in metastatic GC setting which should be approached with caution due to independent simulation of paired DFS/PFS and PPS durations from the illness-death model and the lack of data-driven lower bounds on pre-progression death probability in the metastatic setting.

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P-57 An observational/translational study of BRAF inhibitor combination therapy for BRAF-mutant metastatic colorectal cancer including biomarker research: BEETS trial (JACCRO CC-18)

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Background: BRAF inhibitor combination therapy became the standard of care for BRAF -mutated metastatic colorectal cancer (mCRC) based on the BEACON CRC trial, which showed a survival benefit of the three-drug combination regimen with BRAF and MEK inhibitors plus anti-EGFR antibody as well as the two-drug combination regimen with BRAF inhibitor and anti-EGFR antibody over standard chemotherapy. The two-drug combination regimen is approved in Europe and the US, while both three- and two-drug combination regimens are approved in Japan. These two regimens have not been directly compared in terms of efficacy and the patients and disease factors that guides regimen selection are not clearly established.

Trial design: This is a multicenter observational/translational study to prospectively evaluate the efficacy and safety of BRAF inhibitor combination therapy as a second- or third-line treatment in patients with BRAF -mutant mCRC in clinical practice. Two hundred patients will be assigned to either two- or three-drug combination therapy arm based on physician's choice. Clinical data from the three- and the two-drug combination therapies will be compared to identify factors associated with the benefit of each treatment. Eligibility criteria are (1) patients with colorectal cancer confirmed as adenocarcinoma on pathological examination and with BRAF mutation on tumor tissue-based genomic testing, (2) patients planning to receive BRAF inhibitor combination therapy as second or third-line treatment, (3) patients with ECOG Performance Status (PS) of 0-2, (4) patients must be at least 20 years of age at the time of consent, and (5) patients have measurable or evaluable lesions in RECIST v1.1. The primary endpoint is overall survival. The secondary endpoints include response rate, disease control rate, tumor volume reduction, time to response, duration of response, progression-free survival, and safety. In addition, blood samples of patients will be prospectively collected before and after treatment, which will be used for liquid biopsy research including circulating tumor-DNA (ctDNA) and RNA analyses using next-generation sequencers to explore novel predictors of response and resistance mechanisms to BRAF inhibitor combination therapy. In the translational study part, the primary endpoint is to analyze the association between clinical outcome of BRAF inhibitor combination therapy and tumor genomic data from ctDNA and RNA analysis at pre-treatment. The secondary endpoints are to analyze the association between clinical outcome of BRAF inhibitor combination therapy and liquid biopsy data after failure or intolerance to the treatment; to analyze tumor dynamics by comparing genomic data before and after BRAF inhibitor combination therapy; and to evaluate the association between liquid biopsy data and patient background factors (PS, number of metastatic organs, CRP, presence of primary tumors). Blood-based tumor genomic measurements will be performed by DNA Chip Research Inc (Tokyo, Japan). ctDNA exome analysis will be performed for plasma and tumor-educated blood platelets (TEP)-Seq RNA analysis will be performed for tumor-related platelets which are extracted from blood samples. Enrollment opened in October 2021.

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