P-79 Precision oncology without biomarkers: Assessing drug sensitivity in patient-derived tumoroids to guide mCRC 3rd line therapy

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Background: "Precision Oncology" refers to strategies and tools to find the best treatment for a specific patient. This concept is often reduced to the combination of targeted therapies with molecular biomarkers. Nevertheless, most options indicated in guidelines for 3rd line treatment of mCRC patients do not have associated biomarkers. In vitro assessment of tumor drug sensitivity based on patient-derived 3D tumoroids can be used to guide therapy decision-making. Furthermore, it can inform the "off label" use of drugs susceptible of improving patient's PFS. We have checked the feasibility of such approach.

Methods: Core needle biopsies from mCRC patients having failed at least two treatment lines were collected and shipped fresh to 2cureX labs. Following the IndiTreat® [2cureX, Copenhagen] protocol, the biopsies were mechanically disrupted, and the resulting fragments were cultured to form 3D tumoroids. These tumoroids were added to pre-loaded gel arrays containing the drugs of interest (FOLFOX, FOLFIRI, FOLFOXIRI, regorafenib, trifluridine + tipiracil, mitomycin C + 5FU, gemcitabine + 5FU, temozolomide + irinotecan). Tumoroid growth was assessed after seven days by capturing the images of day 0 and day 7 and comparing them to those of untreated tumoroids, used as negative controls. A proprietary convolutional neural network (IndiNet) translated the images into a growth inhibition (G.I.) score that was used to assign each tumor to a category of sensitivity.

Results: The G.I. results obtained with each of the treatments covered a wide range and were assessed for normality by four different methods: Anderson-Darling, Shapiro-Wilk, Kolmogorov-Smirnov and D'Agostino — Pearson. The results allow us to assume a normal distribution, and define four categories based on the mean and standard deviation of each of these cohorts. Categories have been labelled as "L" (low sensitivity: growth inhibition below mean — 1SD), "ML" (mid-low sensitivity: growth inhibition between mean and mean — 1SD), "MH" (mid-high sensitivity: growth inhibition between mean and mean + 1SD) and "H" (high sensitivity: growth inhibition above mean + 1SD). The percentage of cases in each category was (Low / Mid-Low / Mid-High / High): FOLFOX : 19% / 35% / 19%/ 27% FOLFIRI: 17% / 31% / 28% / 24% FOLFOXIRI: 14% / 39% / 25% / 21% Regorafenib: 15% / 33% / 37% / 15% trifluridine / tipiracil: 17% / 24% / 41% / 17% mitomycin C + 5FU: 25% / 13% / 50% / 13% gemcitabine + 5FU: 17% / 40% / 27% / 17% temozolomide + Irinotecan: 5% / 57% / 14% / 24%.

Conclusions: IndiTreat® provides an individual drug sensitivity profile that clearly differentiated between "low sensitivity" and "high sensitivity" tumoroids for each drug in the panel. This information can be used by oncologists to determine if any of the treatments indicated in guidelines can be an option for that patient, or if she might benefit from the off-label use of certain drugs, thus expanding their treatment options and achieving the benefits of personalization even with standard chemotherapy regimens.

Legal entity responsible for the study: The authors.

Funding: Has not received any funding.

Disclosures: J. Thastrup: Shareholder / Stockholder / Stock options: 2cureX; Full / Part-time employment: 2cureX. O. Thastrup: Officer / Board of Directors: 2cureX. G. Hagel: Shareholder / Stockholder / Stock options: 2curex; Full / Part-time employment: 2curex. H. Harling: Officer / Board of Directors: 2curex.

https://doi.org/10.1016/j.annonc.2022.04.169

P-80 A multicenter randomized phase II study comparing CAPOXIRI plus bevacizumab and FOLFOXIRI plus bevacizumab as the first-line treatment for metastatic colorectal cancer: A safety analysis of the QUATTRO-II study

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Background: FOLFOXIRI plus bevacizumab (BEV) is the standard first-line treatment for metastatic colorectal cancer (mCRC) despite its association with a high incidence of neutropenia and diarrhea. In this study, capecitabine (CAP), oxaliplatin (OX), and irinotecan (IRI) (CAPOXIRI) plus BEV are hypothesized to be more feasible than FOLFOXIRI plus BEV, without compromising the efficacy. Here, results of safety analysis in the induction phase are reported in the randomized phase II QUATTRO-II study comparing CAPOXIRI plus BEV and FOLFOXIRI plus BEV as the first-line treatment for mCRC.

Methods: This multicenter, open-label, randomized phase II study enrolled patients with the ECOG performance status of 0 or 1, without previous chemotherapy in the metastatic setting, with adequate organ function, and with UGT1A1 *6/*28 gene polymorphisms of wild-type or single heterozygous. Patients were randomized in a 1:1 ratio to FOLFOXIRI plus BEV (arm A) or CAPOXIRI plus BEV (arm B). As we previously reported, the recommended phase II doses of CAPOXIRI plus BEV were determined as CAP, 1,600 mg/m^2; OX, 130 mg/m^2; IRI, 200 mg/m^2; and BEV, 7.5 mg/kg every 3 weeks from the results of Safety Lead-In of this study. FOLFOXIRI plus BEV or CAPOXIRI plus BEV in the induction phase was continued until 8/6 (arm A/B) cycles (maximum, 12/8 cycles), followed by 5-FU/l-LV plus BEV or CAP plus BEV in the maintenance phase at the investigator's discretion. The primary endpoint was progression-free survival, and secondary endpoints were overall response rate, overall survival, and safety. The completion of the induction phase was defined as meeting both of the following two criteria in all cycles: all drugs are administered (dose reduction was permitted); and the cycle was started within 28 days of the planned start date.

Results: A total of 103 patients (arm A/B, 51/52) were enrolled from June 2020 to June 2021. Baseline patient characteristics (arm A/B), including the median age (range), 60 (38—75)/60 (35—77) years; the ECOG performance status of 0, 46 (90%)/49 (94%); and UGT1A1 *6/*28 gene polymorphisms, wild-type 30 (59%)/29 (56%) were similar between the two treatment arms. At the data cutoff of December 17, 2021, the incidence of grade >3 major adverse events (AEs) in the induction phase was as follows (arm A/B): neutropenia (65%/39%), febrile neutropenia (10%/12%), diarrhea (8%/17%), and anorexia (8%/17%). No treatment-related deaths occurred. Among patients in arms A and B, 26 (51%) and 30 (58%) patients achieved the completion of the induction phase, respectively. The main reasons for incompletion of the induction phase (arm A/B) were treatment discontinuation due to resection (9/9), disease progression (2/5), and adverse events (5/1) and not meeting the definition of completion of the induction phase (6/6).

Conclusions: This safety analysis showed that both CAPOXIRI plus BEV and FOLFOXIRI plus BEV were safe and tolerable with differences in AE incidences and toxicity profiles. The QUATTRO-II study is still in the follow-up phase, and the efficacy data will be reported in next year's scientific meeting.

Clinical trial identification: Trial registration: Clinicaltrials.gov NCT04097444.

Legal entity responsible for the study: The authors.

Funding: Chugai Pharmaceutical Co, Ltd.

Disclosures: T. Masuishi: Honoraria (self): Taiho, Lilly, Chugai, Yakult Honsha. H. Bando: Honoraria (self): Eli Lilly Japan, Taiho pharmaceutical, Ono pharmaceutical; Research grant / Funding (self): Ono pharmaceutical. H. Satake: Honoraria (self): Ono pharmaceutical co., ltd., Daiichi Sankyo Co., Ltd., Eli Lilly Japan Co., Ltd., Merck Bio Pharma Co., Ltd., MSD Co., Ltd., Bayer Co., Ltd., Bristol-Myers Squibb Co., Ltd., Chugai Pharmaceutical Co., Ltd., Sanofi Co., Ltd., Taiho Pharmaceutical Co., Ltd., Takeda Co., Ltd. and Yakult Honsha Co., Ltd.; Research grant / Funding (institution): Ono pharmaceutical co., ltd., Daiichi Sankyo, Takeda Pharmaceutical Co., Ltd., Sanofi, Taiho Pharmaceutical Co., Ltd.. D. Kotani: Honoraria (self): Takeda, Chugai. T. Hamaguchi: Honoraria (self): Chugai; Research grant / Funding (institution): Chugai. Y. Kagawa: Speaker Bureau / Expert testimony: Lilly, Taiho, Yakult, MSD, Bayer, Daiichisankyo, Sanofi, Chugai, Ono, Takeda, Merck. H. Yasui: Honoraria (self): Daiichi Sankyo, Ono