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

J. Thastrup, O. Thastrup, G. Hagel, H. Harling

2cureX, Copenhagen, Denmark

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

T. Masuishi[1], H. Bando[2], H. Satake[3], D. Kotani[2], T. Hamaguchi[4], M. Shiozawa[5], T. Ikumoto[6], Y. Kagawa[7], H. Yasui[8], T. Moriwaki[9], H. Kawakami[10], S. Boku[11], E. Oki[12], Y. Komatsu[13], H. Taniguchi[1], K. Muro[1], M. Kotaka[6], K. Yamazaki[14], T. Misumi[15], T. Yoshino[16], T. Kato[17], A. Tsuji[18]

[1]Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, Japan; [2]Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan; [3]Department of Medical Oncology, Kobe City Medical Center General Hospital, Kobe, Japan; [4]Saitama Medical University International Medical Center, Hidaka, Japan; [5]Department of Gastrointestinal Surgery, Kanagawa Cancer Center, Yokohama, Japan; [6]Gastrointestinal Cancer Center, Sano Hospital, Kobe, Japan; [7]Department of Gastroenterological Surgery, Osaka General Medical Center, Osaka, Japan; [8]Department of Medical Oncology, Kobe City Medical Center General Hospital, Kobe, Japan; [9]Department of Gastroenterology, Faculty of Medicine, University of Tsukuba, Tsukuba, Japan; [10]Kindai University Faculty of Medicine, Osakasayama, Japan; [11]Kansai Medical University, Hirakata, Japan; [12]Department of Surgery and Science, Graduate School of Medical Science, Kyushu University, Fukuoka, Japan; [13]Division of Cancer Center, Hokkaido University Hospital, Sapporo, Japan; [14]Division of Gastrointestinal Oncology, Shizuoka Cancer Center, Sunto-Gun, Japan; [15]Department of Data Science, National Cancer Center Hospital East, Kashiwa, Japan; [16]National Cancer Center Hospital East, Kashiwa, Japan; [17]Department of Surgery, National Hospital Organization, Osaka National Hospital, Osaka, Japan; [18]Department of Clinical Oncology, Kagawa University Hospital, Miki, Japan

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

Pharmaceutical, Taiho Pharmaceutical, Chugai Pharma, Bristol-Myers Squibb Japan, TERUMO, Eli Lilly Japan, Merk Biopharma, Yakult Honsha, Bayer Yakuhin, Takeda Pharmaceutical; Research grant / Funding (self): MSD, Ono Pharmaceutical, Daiichi Sankyo, Astellas Pharma. T. Moriwaki: Speaker Bureau / Expert testimony: Taiho Pharmaceutical, Chugai Pharma; Research grant / Funding (institution): Taiho Pharmaceutical, Chugai Pharma. H. Kawakami: Honoraria (self): Taiho Pharmaceutical Co. Ltd, Ono Pharmaceutical Co. Ltd., Bristol-Myers Squibb Co. Ltd., Daiichi-Sankyo Co. Ltd.; Advisory / Consultancy: Daiichi-Sankyo Co. Ltd.; Research grant / Funding (institution): Taiho Pharmaceutical Co. Ltd, Bristol-Myers Squibb Co. Ltd, Eisai Co. Ltd., Kobayashi Pharmaceutical. Co., Ltd.. Y. Komatsu: Speaker Bureau / Expert testimony: TAIHO Phamaceutical Co., Ltd., yakult; Research grant / Funding (institution): TAIHO Phamaceutical Co., Ltd., CHUGAI Phamaceutical Co., Ltd.. H. Taniguchi: Honoraria (self): Takeda, Taiho, Merck Biopharma; Research grant / Funding (institution): Daiichi-Sankyo, Sysmex, Takeda. K. Muro: Honoraria (self): Eli Lilly, Chugai, Takeda, Ono, Taiho, Sanofi, Bristol-Myers Squibb, and Bayer; Advisory / Consultancy: Amgen, AstraZeneca, Ono, and Chugai; Research grant / Funding (institution): Astellas, Amgen, Solasia Pharma, Sanofi, Daiichi Sankyo, Parexel International, Taiho, MSD, Merck Biopharma, Pfizer, Eisai, Novartis, and Ono . M. Kotaka: Honoraria (self): Chugai pharmaceutical, Lilly. K. Yamazaki: Honoraria (self): Chugai Pharma, Takeda, Taiho; Research grant / Funding (institution): Taiho Pharmaceutical. T. Yoshino: Honoraria (self): Taiho Pharmaceutical, Chugai Pharmaceutical, Eli Lilly, Merck Biopharma, Bayer Yakuhin, Ono Pharmaceutical and MSD; Research grant / Funding (institution): Ono Pharmaceutical, Sanofi, Daiichi Sankyo, PAREXEL International, Pfizer Japan, Taiho Pharmaceutical, MSD, Amgen, Genomedia, Sysmex, Chugai Pharmaceutical and Nippon Boehringer Ingelheim. T. Kato: Honoraria (self): CHUGAI PHARMACEUTICAL CO., LTD, ONO Pharmaceutical Co, Eli Lilly and Company; Honoraria (Institution): CHUGAI PHARMACEUTICAL CO., LTD,; Research grant / Funding (self): ONO Pharmaceutical Co; Research grant / Funding (institution): ONO Pharmaceutical Co. A. Tsuji: Speaker Bureau / Expert testimony: Taiho Pharmaceutical Co., Ltd. , Chugai Pharmaceutical Co., Ltd. , Eli Lilly Japan Co., ; Research grant / Funding (institution): Taiho Pharmaceutical Co., Ltd. , Sanofi Corporation, Ono Pharmaceutical Co.,. All other authors have declared no conflicts of interest.

https://doi.org/10.1016/j.annonc.2022.04.170

P-81 Phase 3 study of MK4280A (coformulated favezelimab and pembrolizumab) versus standard of care in previously treated PD-L1−positive metastatic colorectal cancer (mCRC)

T. Kim[1], J. Taieb[2], M. Passhak[3], T. Kim[4], S. Kim[5], R. Geva[6], E. Hofsli[7], G. Perl[8], S. Yalcin[9], A. Hubert[10], B. Somer[11], Z. Wong[12], A. Wang[13], P. Leconte[14], D. Fogelman[13], V. Heinemann[15]

[1]Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; [2]Department of Gastroenterology and Gastrointestinal Oncology, Hôpital Européen Georges-Pompidou, AP-HP, Université de Paris, Paris, France; [3]Rambam Medical Health Care Campus, Haifa, Israel; [4]Seoul National University, Seoul, South Korea; [5]Samsung Medical Center, Seoul, South Korea; [6]Tel Aviv University and Tel Aviv Sourasky Medical Center, Tel Aviv, Israel; [7]Department of Oncology, Trondheim University Hospital, Trondheim, Norway; [8]Rabin Medical Center, Petah Tikva, Petah Tikva, New Zealand; [9]Hacettepe Universitesi, Ankara, Turkey; [10]Hadassah Ein Kerem Medical Center, Jerusalem, Israel; [11]West Cancer Center, University of Tennessee, Germantown, United States; [12]Frankston Hospital & Peninsula Clinical School, Monash University, Melbourne, Frankston, Australia; [13]Merck & Co., Inc., Kenilworth, United States; [14]MSD France, Puteaux, France, Paris, France; [15]Department of Hematology and Oncology, University of Munich (Ludwig Maximilian University), Munich, Germany

Background: Immune checkpoint (IC) inhibitors are effective in mismatch repair-deficient or microsatellite instability-high colorectal cancer (CRC). However, for mismatch repair-proficient (pMMR) mCRC, which account for 95% of mCRC tumors, treatment options are limited. In patients with CRC, LAG-3 is overexpressed on colorectal immune cells and correlated with poor differentiation, advanced stage, lymph node involvement and invasion depth (Chen J, Zihua C. Med Oncol. 2014; 31:82). As such, LAG-3 represents a rational target for IC inhibition in CRC. IC inhibitor combination therapy with MK4280A, a coformulation of anti−LAG3 antibody favezelimab and pembrolizumab, has shown promising antitumor activity and a manageable safety profile in patients with PD-L1 CPS≥1 microsatellite stable mCRC and may be efficacious in pMMR mCRC (Garralda E et al. J Clin Oncol. 2021;39. Abstract 3584). In this ongoing phase 3 study (NCT05064059), we will evaluate the efficacy and safety of MK-4280A in patients with PD-L1−positive pMMR mCRC.

Trial design: The open-label, parallel group, active-controlled study plans to enroll approximately 432 patients aged ≥18 years with histologically confirmed unresectable mCRC, pMMR and PD-L1 CPS ≥1 tumors, and measurable disease per RECIST v1.1 by investigator review. All patients must have experienced progressive disease after: 1) fluoropyrimidine, irinotecan and oxaliplatin, with or without anti-VEGF antibody, anti−EGFR antibody for patients with left-sided tumors that are RAS WT, and 2) RAF inhibitor with or without binimetinib in patients with BRAF v600E mutations. Key eligibility criteria include ECOG status 0 or 1, adequate organ function, and availability of archival or newly obtained tissue sample to assess PD-L1 and MMR status. Patients will be randomly assigned to MK-4280A (coformulated favezelimab 800 mg/pembrolizumab 200 mg; Arm A) IV Q3W or standard of care (Arm B) (regorafenib 160 mg PO Q4W [QD on days 1-21; no dose on days 22-28] or TAS-102 35mg/m^2 PO Q4W [BID on days 1-5 and 8-12; no dose on days 6, 7, and 13-28]). Patients will be stratified by geographic region (Asia Pacific, EMEA/Americas), presence of liver metastases (yes, no) and time from initial diagnosis of mCRC to randomization (≥18 mo, < 18 mo). Treatment will continue for ≤35 cycles of MK-4280A or unacceptable toxicity, disease progression, confirmed CR with MK-4280A must have been treated for ≥8 cycles and have received 2 cycles after the initial CR was observed (Arm A), or withdrawal from study. Disease assessment by CT or MRI will be performed Q9W during the study. Primary end point is overall survival (OS). Secondary end points are progression free survival (PFS), objective response rate (ORR) and duration of response (by blinded independent central review per RECIST v1.1), patient-reported outcomes on health-related quality of life, and safety graded per NCI CTCAE v5.0. OS and PFS will be estimated by Kaplan-Meier methods. ORR with 95% CI will be estimated using the Clopper-Pearson method.

Clinical trial identification: ClinicalTrials.gov, NCT05064059.

Legal entity responsible for the study: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

Funding: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

Disclosures: T. Kim: Research grant / Funding (institution): Genentech, AstraZeneca, Sanofi-Aventis. R. Geva: Honoraria (self): MSD; Advisory / Consultancy: MSD. S. Yalcin: Honoraria (self): Pfizer, Merck Serono, Gen ilac, Amgen, Novartis, Abbott, Natera; Advisory / Consultancy: Pfizer, Merck Serono, Amgen, Abbott; Speaker Bureau / Expert testimony: Gen ilac, Eczacibasiıı, Amgen, Merck Serono, Roche, Abbott; Travel / Accommodation / Expenses: Gen ilac, Amgen, Roche. A. Wang: Full / Part-time employment: Merck & Co., Inc. P. Leconte: Shareholder / Stockholder / Stock options: MSD; Full / Part-time employment: MSD. D. Fogelman: Shareholder / Stockholder / Stock options: Merck, GTX; Full / Part-time employment: Merck. V. Heinemann: Honoraria (self): Merck, Amgen, Roche, Sanofi, SIRTEX, Servier, Pfizer, Pierre-Fabre, Astra-Zeneca; Advisory / Consultancy: Merck, Amgen, Roche, Sanofi, SIRTEX, BMS; MSD, Novartis, Boehringer Ingelheim, Servier, Pierre-Fabre, Celgene, Terumo; Research grant / Funding (institution): Merck, Amgen, Roche, Sanofi, Pfizer, Boehringer-Ingelheim, Sirtex, Bayer, Servier; Travel / Accommodation / Expenses: Merck, Roche, Amgen, SIRTEX, Bayer, Servier. All other authors have declared no conflicts of interest.

https://doi.org/10.1016/j.annonc.2022.04.171

P-82 Evaluation of prognostic tools in locally advanced rectal cancer patients treated with neoadjuvant chemoradiotherapy

P. Gómez Mugarza[1], E. Polo[1], B. López Roldán[1], S. Barriendos Sanz[1], M. Monreal Cepero[1], S. Campos Ramírez[1], F. Mocha Campillo[1], P. Trincado Cobos[1], A. Comin[1], J. Ponce[1], V. Navarro Aznar[1], I. Gurruchaga Sotés[2], A. Nuño Alves[3], M. Felices Lobera[4], V. Alonso Orduña[1]

[1]Hospital Miguel Servet, Zaragoza, Spain; [2]Complejo Hospitalario de Navarra, Pamplona, Spain; [3]Hospital Obispo Polanco, Teruel, Spain; [4]Hospital Comarcal Alcañiz, Alcañiz, Spain

Background: Neoadjuvant chemoradiotherapy (NCR) has become the standard of treatment for patients with locally advanced rectal cancer (LARC). Several prognostic tools such as Neoadjuvant Rectal (NAR) score, Tumor Regression grade (TRG), pathological staging or Downstaging have been developed. However, inconsistent findings among different studies have been shown, therefore their prognostic value has not been validated. Our aim is to find prognostic factors for Overall Survival (OS) and Disease-Free-Survival (DFS) in a cohort of LARC patients.

Methods: A total of 385 LARC patients treated with NCR between 2000 and 2019 were included. Epidemiologic and tumor characteristics were studied. NAR score, TRG and Downstaging were calculated. Kaplan-Meier curves and univariate Cox regression were calculated for both OS and DFS. Finally, multivariate analysis using Cox regression model was performed.

Results: Of the 385 patients, 66.8% were males and median age was 66 years old. The main cT stage was T3 with 88,6% of cases and 41.6% cN2. 90.6% of patients underwent treatment with concomitant radiotherapy and capecitabine. Median follow-up was 79 months. At the time of analysis, 28.8% of patients had died. Median OS was not reached, and median DFS was 178 months. 110, 188 and 85 patients were classified as low, moderate and high-risk NAR group respectively. 10-year-OS rates were 74.9%, 69.9%, and 47.1% in low, moderate and high-risk NAR groups respectively. HR comparing moderate and low group was 1.5 (p=0.13), and 3.05 (p<0.001) between high and low NAR. 10-year-DFS rates were with 72.8%, 60% and 44.4% respectively, with HR 1.85 (p=0.01) and 3.26 (p<0.001) comparing moderate and high with low-risk NAR groups respectively. 10-year-OS rates were 78% in patients with pCR, 65.4% minimal-moderate response and 54.8% if no response was observed. HR comparing pCR and moderate-minimal response was 1.75 (p=0.63) and 2.75 (p=0.003) between pCR and no response. 10-year-DFS rates were 75.1%, 59.1% and 44.9% for pCR, moderate-minimal and no response, HR 1.89 (p=0.019) between moderate-minimal response and pCR and HR 2.85 (p=0.001) between no response and pCR. 10-year-OS rates were 70.6% and 51.9% in patients with positive and negative Downstaging respectively, HR 1.98 (p=0.001). 10-year-DFS rates were 64.9% and 42.2% respectively HR 2.19 (p<0.001). Only age (p < 0,001), NAR group (p < 0.001) and R0 resection (p=0.017) remained as independent prognostic factors for OS at multivariate analysis. Evidence for R0 resection (p < 0.001), Downstaging (p < 0.001), age (p=0.007) and diagnostic CEA levels (p=0.036) as independent prognostic factors for DFS was also proved.

Conclusions: Among all the analyzed tools, only NAR score has shown evidence real prognostic value for OS, as well as Downstaging for DFS. These findings could help oncologists in deciding convenience for further post-resection treatment or stricter follow-up.

Legal entity responsible for the study: The authors.

Funding: Has not received any funding.

Disclosures: V. Alonso Orduña: Advisory / Consultancy: SERVIER, MERCK, AMGEN; Travel / Accommodation / Expenses: IPSEN. All other authors have declared no conflicts of interest.

https://doi.org/10.1016/j.annonc.2022.04.172