Circulating tumor DNA for early release detection and monitoring disease status in patients with early-stage pancreatic adenocarcinoma

M. Abdelrahim1, A. Esmai1, T. Katz1, S. Sharma3, E. Kalashnikova2, M. Malhotra3, P. Osham4, P. Billings4, A. Aleshin4

1Houston Methodist Hospital, Houston, United States; 2Natera, Inc., San Carlos, United States

Background: Pancreatic adenocarcinoma (PDAC) is one of the most aggressive cancer histologies, as evidenced by high recurrence rate (85%) and poor 5-year overall survival of 9%. Numerous circulating biomarkers have been evaluated for the detection of molecular monitoring and residual disease (MRD) detection in PDAC; however, the application of these techniques has been limited in early-stage PDAC due to poor sensitivity and specificity. Recently, an ultrasonic, personalized, and tumor-informed ctDNA assay (Signatera TM) has been shown to overcome many of these challenges that have limited the clinical utility of the aforementioned biomarkers, for the first time allowing for reliable MRD detection in PDAC and other histologies.

Methods: In this cohort, 7 patients with pancreatic cancer and 1 patient with ampullary adenocarcinoma were prospectively enrolled for ctDNA analysis and followed up for a median of 316 days (range: 152-684). Personalized mutational profiles derived from ctDNA were compared to tissue-sequencing whole-exome sequencing (WES) in 5 patients. Specific ctDNA assays for variant detection in plasma samples. Apart from ctDNA analysis, patients were also monitored using carcinoembryonic antigen (CEA), cancer antigen 19-3 (CA-19-3), and radiological imaging.

Results: In these 8 cases of resectable pancreatic/ampullary adenocarcinoma, 7 patients received mFOLFIRINOX adjuvant chemotherapy and 2 received additional rounds of gemcitabine/oxaliplatin and gemcitabine/paclitaxel. Three patients had plasma collected after surgery, of which 2 patients (MRD rate of 66%) were found to be the investigational site of re-remaining disease. During the course of the follow-up, 50% (4/8) of patients relapsed, of which 100% had ctDNA detected prior or at the time of recurrence (100% sensitivity). The presence of ctDNA was associated with reduced recurrence-free survival (HR: 10.14; 95% CI: 1.07 - 134.79; p = 0.03). ctDNA findings were found to correlate with imaging and preceding imaging results. However, CA 19-9 and CEA, in certain cases showed discordance with imaging and were found to be elevated due to other conditions, such as gastritis.

Conclusions: Our findings suggest, presence of ctDNA after surgery in early-stage PDAC is associated with reduced recurrence-free survival. During monitoring, ctDNA was found to be a better prognostic marker compared to CA-19-9 and CEA and can be used to inform on disease status prior to imaging.

Legal entity responsible for the study: The authors.

Funding: Has not received any funding.


https://doi.org/10.1016/j.annonc.2021.05.163

References

Annals of Oncology

Abstracts

Conclusion: Cytosponge TM-based assessment of post-CRT response is feasible, has low toxicity, and high acceptance. The detection of atypia and/or aberrant p53 on Cytosponge in cases with negative histology on endoscopic biopsies suggests that this pan-oesophageal sampling method may add value. Larger studies are required to test its role in post-treatment surveillance, either as adjunct or alternative to endoscopy.

Clinical trial identification: ClinicalTrials.gov identifier: NCT03529669.

Acknowledgment: This work was funded by Oncology Clinical Trials Office, Department of Oncology, University of Oxford, in collaboration with Oxford Clinical Trials Research Unit and The Centre for Statistics in Medicine, University of Oxford. Cytosponge® provided by Cambridge University Hospitals NHS Foundation Trust.

Legal entity responsible for the study: Oxford University Department.

Funding: Cancer Research UK (C28585/A22173).

Disclosure: S. Levy: Full / Part-time employment: University of Oxford. R. Fitzgerald: Licensing / Royalties: Medronic. All other authors have declared no conflicts of interest.

https://doi.org/10.1016/j.annonc.2021.05.164

P-110

Is dexamethasone necessary as a prophylactic antiepileptic prior to gemcitabine plus nab-paclitaxel therapy?

S. Murata1, M. Takeno1, H. Imakura2, K. Morimichi1, J. Tauchi1, H. Suzuki1, T. Kawasaki1, H. Egami1, K. Goda1, K. Hayashi1, T. Okada1, T. Shibuki1, K. Watanabe1, S. Miyazawa1, M. Sasaki1, Y. Hashimoto1, S. Mitsunaga1, M. Ikeda3

1National Cancer Center Hospital East, Kashiwa, Japan; 2National Cancer Center East, Kashiwa, Japan; 3National Cancer Center Hospital East, Kashiwa, Japan

Background: Gemcitabine plus nab-paclitaxel (GnP) is widely used as one of the first-line treatments in Japan for patients with advanced pancreatic cancer (APC). Chemotherapy-induced nausea and vomiting (CINV) is one of the most debilitating adverse effects of this treatment and is often reported as the leading cause of treatment discontinuation. Thus, GnP is ranked as a moderately emetogenic chemotherapeutic (MEC) in Japan, and patients receiving this therapy are routinely administered dexamethasone (DEX) 6.6 mg plus granisetron 1 mg as prophylactic agents against CINV. In some APC patients with diabetes mellitus (DM), DEX is sometimes administered at a reduced dose or omitted altogether, to avoid steroid-induced hyperglycemia. However, the frequency and degree of CINV in APC patients with diabetes mellitus receiving GnP therapy has not yet been fully evaluated.

Methods: The study subjects were APC patients who received GnP as the first-line treatment from March 2017 to May 2020 at our hospital. The patients were divided into two groups according to whether they received DEX or not: the DEX-on group (6.6 mg or 3.3 mg) and the DEX-off group. The efficacy against CINV (complete response (CR) rate; no vomiting and no rescue therapy, complete control (CC) rate; CR plus rescue therapy) and the occurrence of DEX-induced adverse effects were compared between the two groups.

Results: Among the total of 234 patients who received first-line GnP treatment during the period, 35 patients were included into the DEX-on group, and 199 patients into the DEX-off group, respectively. Significant differences between the two groups (DEX-on vs. DEX-off) were seen in the frequency of use of 5-HT3 blockers (granisetron/pegvisomant, 194/5 vs. 21/14, p < 0.05), dose reduction of chemotherapy at the first administration of GnP (8/191 vs. 3/10, p = 0.03) and presence of DM (50/149 vs. 33/2, p = 0.05). On the other hand, there was no significant difference in the antiemetic efficacy between the two groups (DEX-on vs. DEX-off): CR rate, 80% vs. 86%, p = 0.03; CC rate, 79% vs. 86%, p = 0.38; CT rate, 77% vs. 86%, p = 0.243. Multivariate logistic regression analysis identified age < 55 years (odds ratio [OR], 2.69; p = 0.02), female sex (OR, 1.93; p = 0.03) and presence of DM (OR, 2.69; p = 0.02) as significant factors associated with an increased risk of TC failure.

Conclusions: Withholding of DEX as prophylactic medication against CINV was not significantly associated with an increased incidence of CINV in APC patients receiving GnP therapy. Thus, DEX-off GnP is a valid option in APC patients with DM.

Legal entity responsible for the study: The author.

Funding: No further funding received.

Disclosure: H. Imakura: Honoria (self): Yakult Honsha, AstraZeneca, Nihon Servier; Advisory / Consultancy: Nihon Servier; Research grant / Funding (self): Ono Pharmaceutical. M. Ikeda: Honoria (self): Eli Lilly Japan, Nihon Servier; Taiho Pharmaceutical, Yakult; Advisory / Consultancy: Eli Lilly Japan, Nihon Servier; Research grant / Funding (institution): Nihon Servier. All other authors have declared no conflicts of interest.

https://doi.org/10.1016/j.annonc.2021.05.165

P-111

PERSPECTIVE: Tepotinib plus cetuximab in patients with RAS/BRAF wild-type left-sided metastatic colorectal cancer and acquired resistance to anti-EGFR antibody therapy due to MET amplification


1Vall d’Hebron University Hospital and Vall d’Hebron Institute of Oncology (VHIO), Barcelona, Spain; 2Mayo Clinic Phoenix, Phoenix, United States; 3Medical Oncology Department, Hospital Universitario, Valencia University, Ciberonc, Spain; 4NM Universidadiario Sanchinarro. Centro Integral Oncológico Clara Campo ( HM CIIOC), Madrid, Spain; 5Hospital Universitario 12 de Octubre, IMAS12, CNIO, CIOCA, Madrid, Spain; 6Department of Medical Oncology, Hospital Universitario Virgen del Rocio, Sevilla, Spain; 7Hospital Universitario La Paz, Madrid, Spain; 8CHU Hospital Henri Mondor, APHP, UPEC, Créteil, France; 9Department of Medical Oncology, University Hospital of Besançon, Besançon, France; 10The University of Texas MD Anderson Cancer Center, Houston, United States; 11Allegeny Health Network Cancer Institute, Pittsburgh, Pennsylvania, United States; 12Division of Medical Oncology, Department of Medicine, Duke University Medical Center, Durham, United States; 13Merck KGaA, Darmstadt, Germany; 14University Hospital Marques de Valdecilla, IDIVAL, Santander, Spain

Background: MET amplification (METamp) is a secondary, or co-driving, genetic change in patients with metastatic colorectal cancer (mCRC) and acquired resistance to anti-EGFR therapy, which can contribute to disease progression. In EGFR-resistant patients with mCRC and METamp, MET inhibition plus an anti-EGFR agent may achieve disease control by targeting emerging MET pathway activation and maintaining EGFR pathway inhibition. Tepotinib is an oral, once-daily, highly selective, patient-tailored MET tyrosine kinase inhibitor (TKI) that has been approved by the Japanese Ministry of Health, Labour and Welfare for NSCLC harboring MET exon 14 skipping. Tepotinib plus gefitinib has shown improved outcomes in patients with EGFR-mutant MET NSCLC and acquired EGFR TKI resistance versus chemotherapy (INSIGHT: NCT01982955). In these patients, progression-free survival (PFS) was 16.4 vs 4.2 months (HR = 0.13; 90% CI: 0.04, 0.43) and overall survival (OS) was 37.3 vs 13.1 months (HR = 0.80; 90% CI: 0.67, 0.95). In patients with mCRC and acquired resistance to anti-EGFR antibody therapy due to METamp, tepotinib plus anti-EGFR antibody cetuximab may be active and provide an effective therapeutic option.

Trial design: This Phase II, multicenter, single-arm, open-label study will assess preliminary safety and tolerability, antitumor activity, and explore pharmacokinetic profiles of tepotinib plus cetuximab in patients with RAS/BRAF wild-type left-sided mCRC, and acquired resistance to anti-EGFR antibody-targeted therapy due to METamp (EUDRACT: 2021-000515934). After a safety run-in period (6–12 weeks; dose-limiting toxicities), the Safety Monitoring Committee will determine the recommended Phase II dose (RP2D) of tepotinib to be used in combination with cetuximab. Enrollment is based on a confirmed advanced left-sided CRC diagnosis (RAS/BRAF wild-type), documented previous anti-EGFR therapy and acquired resistance to the most recent anti-EGFR antibody, and METamp confirmed by liquid and/or tissue biopsy. Patients must be ≥18 years old, have an Eastern Cooperative Oncology Group performance status of 0/1 and normal organ function. The study will screen at least 35 patients to account for METamp heterogeneity in this treatment setting. The study is being conducted at centers in Belgium, Czech Republic, France, Italy, Russia, Spain, the UK, and the US. As of March 2021, there are 15 active centers in Spain (7 centers), France (5 centers) and the US (3 centers). Approximately 42 patients are planned to receive treatment at the RP2D in Cohort 2 (second-line, outside the US) and 20 in Cohort B (third-line, US only). Primary endpoint: investigator-assessed objective response (RECIST 1.1). Secondary endpoints are investigator-assessed duration of response (DoR), progression-free survival (PFS) (RECIST 1.1), overall survival, tolerability and safety (adverse event grading will be based on NCI-CTCAE v5.0), and cetuximab immunogenicity (measured by antidrug antibody assays at the start and end of treatment). Additional endpoints include assessment of cetuximab and cetuximab pharmacokinetic profiles, and expression of resistance biomarkers related to MET (from blood and/or tissue samples). Retrospective assessment of best overall response, DoR, and PFS by an independent review committee may be conducted. No formal statistical hypothesis will be tested in this exploratory study.

Clinical trial identification: NCT04515394.

Editorial acknowledgment: Medical writing assistance (funded by Merck KGaA, Darmstadt, Germany) was provided by Syneos Health, London, UK.

Legal entity responsible for the study: Merck KGaA, Darmstadt, Germany.

Funding: Merck KGaA, Darmstadt, Germany.

Disclosure: J. Tabernero: Honoria (self): educational collaboration with Imedex, Medscape Education, MH Life Sciences, PeerView Institute for Medical Education and Physicians Education Resources; Advisory / Consultancy: Nihon Servier; Research grant / Funding (self): Ono Pharmaceutical. M. Ikeda: Honoria (self): Eli Lilly Japan, Nihon Servier; Taiho Pharmaceutical, Yakult; Advisory / Consultancy: Eli Lilly Japan, Nihon Servier; Research grant / Funding (institution): Nihon Servier. All other authors have declared no conflicts of interest.

https://doi.org/10.1016/j.annonc.2021.05.165