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Biomarkers, Others

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Moderator : Akihito Tsuji (Department of Clinical Oncology, Kagawa University Faculty of Medicine)
Discussant : Katsuya Tsuchihara (Exploratory Oncology Research and Clinical Trial Center, National Cancer Center)

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Detection of circulating tumor DNA (ctDNA) in untreated patients (pts) with cancer : implications for early cancer detection
Takayuki Yoshino (Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East)

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Molecular Determinants of Efficacy with Futibatinib for Advanced Solid Malignancies with FGFR Alterations in Circulating Tumor DNA : TiFFANY, A GOZILA-affiliated Trial
Eiji Shinozaki (Gastroenterological Chemotherapy Division, The Cancer Institute Hospital)

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Efficacy of biomarker-matched therapy in clinical trials for advanced solid tumors : a pooled analysis of SCRUM-Japan GI-SCREEN, GOZILA, and MONSTAR
Tadayoshi Hashimoto (Translational Research Support Office, National Cancer Center Hospital East/Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East)

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Predictive factors for treatment-related adverse events and clinical response in anamorelin treatment : an interim analysis of post-marketing all-case surveillance
Koichi Takayama (Department of Pulmonary Medicine, Graduate School of Medical Science, Kyoto Prefectural University of Medicine)

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FR4-1

Detection of circulating tumor DNA (ctDNA) in untreated patients (pts) with cancer : implications for early cancer detection

Takayuki Yoshino [1], Antony Tin [2], Shifra Krinshpun [3], Breeana Mitchell [3], Sara Bristow [2], Alexey Aleshin [3], Minetta Liu [2], Mark Jesus Magbanua [4], Laura Van't Veer [4], Jocelyn Chapman [5], Daniel Tan [6], Claus Lindbjerg Andersen [7,8], Yoshiaki Nakamura [1]

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Background: Blood-based early cancer detection is an emerging tool to identify cancer signals in asymptomatic individuals. We report on pretreatment ctDNA detection rates in cancer pts and in correlation with median tumor mutational burden (mTMB) rates.

Methods: Pretreatment plasma samples were analyzed via a tumor-informed ctDNA test (Signatera ™) in 1657 pts with breast cancer (BC, N=131) , lung cancer (LC, N=57) , colorectal cancer (CRC, N=1382) , epithelial ovarian cancer (OV Stage-agnostic, exome-based mTMB was reported (BC, CRC, PC, DLBCL, LC) , pancreatic cancer (PC, N=17) , or diffuse large B cell lymphoma (DLBCL, N=37) ., internal data, OV pmid35087563) .

Results: Baseline ctDNA was detected in 1621 (87 %) pts (stage I/II 707/858, 82.4 %; III/IV 914/998, 91.6 %) . In BC (mTMB 4.4 mut/MB) , ctDNA rates were lower in hormone receptor -positive tumors (stage I/II 61.2 % [74/121] , III 81 % [17/21]) vs triple negative BC (I/II 81.5 % [75/92] , III 97 % [58/60]) and HER2+ tumors (I/II 73.9 % [17/23] , III 87.5 % [7/8]) . In LC, ctDNA rates were lower in adenocarcinoma (mTMB 6.0 mut/MB; I/II 25 % [5/20] , III 73 % [11/15]) vs squamous cell carcinoma (mTMB 7.2 mut/MB; I/II 85 % [11/13] , III 100 % [9/9]) . In CRC (mTMB 4.31 mut/ MB, bi-modal distribution) , ctDNA rates for stage I/II/III-IV were [(74 % (71/96) , 94 % (421/448) and 92 % (773/838)] . In OV (mTMB 1.9 mut/MB) , ctDNA rates were 60 % (9/15) in stage I/II and 72 % (15/21) in stage III/IV. In PC (mTMB 1.47 mut/MB) , ctDNA rates were 65 % (11/17) in stage I/II and 100 % (2/2) in stage III/IV. In DLBCL (mTMB 3.56 mut/MB) , ctDNA rates were 100 % (13/13) in stage I/II and 92 % (22/24) in III/IV.

Conclusions: Our large study supports past findings that ctDNA positivity varies by cancer and histology and is higher in some later stage cancers and suggests that presurgical ctDNA can be detected in most patients with a tumor-informed approach. Further studies are needed to understand biological and technical factors that may impact assay performance.

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FR4-2

Molecular Determinants of Efficacy with Futibatinib for Advanced Solid Malignancies with FGFR Alterations in Circulating Tumor DNA : TiFFANY, A GOZILA-affiliated Trial

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Background: *FGFR* alterations are observed in approximately 7 % of advanced solid malignancies. Optimal therapeutic strategies with FGFR inhibitors for *FGFR*-altered tumors are yet to be defined.

Methods: We conducted a multicenter, investigator-initiated, phase II basket-type trial, TiFFANY, to evaluate the efficacy and safety of futibatinib, a highly selective covalent pan-FGFR inhibitor, in twenty-six patients (pts) with advanced solid malignancies with *FGFR* alterations identified by ctDNA analysis who were refractory or intolerant to standard-of-care treatment. Blood and tissue samples collected before treatment (baseline), at week-3, and after disease progression were analyzed for biomarker analysis.

Results: Five pts with *FGFR* alterations (*FGFR3* mutation, 2; *FGFR2* amplification, 2; *FGFR2* fusion, 1) in various cancer types (biliary tract, gastric, urothelial, and urachal cancer) achieved a confirmed response (19.2 %; 95 % CI, 6.6-39.4 %). ctDNA fraction was significantly decreased at week-3 in these responders. Pts with no concurrent RTK/RAS/PI3K and cell cycle alterations in ctDNA significantly responded to futibatinib than those with at least one of these alterations (objective response rate 50 % vs. 0 %; P=0.0038). Acquired gene alterations in ctDNA after progression tended to be more common in pts with *FGFR* amplification (83.3 %) than in those with *FGFR* mutation or fusion (60 % or 66.7 %). Single-cell RNA sequencing using pre- and post-treatment tumor tissue samples from a patient with *FGFR2*-amplified gastric cancer who had a tumor shrinkage revealed downregulated *FGFR2* expression and proliferation of clusters with different gene signatures after progression.

Conclusions: Futibatinib demonstrated promising efficacy in refractory advanced solid malignancies with *FGFR* alterations in ctDNA. ctDNA genotyping may be useful in assessing biomarkers such as oncogenic co-alterations and resistance mechanisms to futibatinib.

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FR4-3

Efficacy of biomarker-matched therapy in clinical trials for advanced solid tumors : a pooled analysis of SCRUM-Japan GI-SCREEN, GOZILA, and MONSTAR

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Background

We have executed the SCRUM-Japan MONSTAR-SCREEN, a nationwide molecular profiling project to facilitate the enrollment of patients (pts) with advanced solid tumors into matched clinical trials based on identified biomarkers. Here, we investigated clinical outcomes of these pts.

Methods

The SCRUM-Japan GI-SCREEN was launched for gastrointestinal cancers in 2015, followed by GOZILA, MONSTAR-SCREEN-1, and MONSTAR-SCREEN-2 for advanced solid tumors. The used profiling assay for genomic alterations was Oncomine Comprehensive Assay for tumor tissue in GI-SCREEN, Guardant360 for plasma in GOZILA, FoundaitionOne CDx for tissue and FoundationOne Liquid CDx for plasma in MONSTAR-SCREEN-1, and CARIS MI Profile for tissue in MONSTAR-SCREEN-2. Pts were treated in clinical trials or practice based on identified biomarkers.

Results

Of 12,716 pts enrolled in our project as of May 22, 2023, 649 (5.1 %) were enrolled in matched clinical trials based on identified biomarkers. The major cancer types that had matched clinical trials included colorectal (n=351), biliary tract (n=66), gastric (n=51), esophageal (n=35), pancreatic (n=27), and prostate cancers (n=16). The objective response rate (ORR), median progression-free survival, and median overall survival (OS) for pts in matched trials were 29 % (95 % CI, 21 % to 37 %), 3.2 months (95 % CI, 2.8 to 3.9 months), and 15.3 months (95 % CI, 13.4 to 16.5). Evaluating by each drug target given to at least 10 patients, therapies targeting HER2 had the highest ORR of 49 %, followed by PD-1/PD-L1 (36 %), MEK (26 %), BRAF (25 %), and MET (24 %). Overall, pts who received matched therapy in clinical trials or practice had significantly longer OS than those who did not (hazard ratio, 0.79; 95 % CI 0.73 to 0.86; P <0.01).

Conclusions

Our nationwide molecular profiling project has facilitated the enrollment of pts with advanced solid tumors in clinical trials. Furthermore, it demonstrated a survival benefit by providing pts matching targeted therapy.

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FR4-4

Predictive factors for treatment-related adverse events and clinical response in anamorelin treatment : an interim analysis of post-marketing all-case surveillance

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Background: Anamorelin (ANA) was approved in Japan in 2021 as the world's first drug for treating cachexia associated with non-small cell lung cancer, gastric cancer, pancreatic cancer, and colorectal cancer. A post-marketing all-case surveillance (PMS) is being conducted to evaluate the real-world safety and effectiveness of ANA.

Methods: This interim analysis included all patients who received ANA on or after April 21, 2021, and whose case report forms were collected by January 21, 2023. We performed multivariate logistic regression to identify predictive factors for hyperglycemia-, hepatic impairment-, or conduction disorders-associated treatment-related adverse events (TRAEs) ; and clinical response. Responders were defined as those with ≧ 3 % body weight increase and ≧ 2-point increase in the 5-item Anorexia Symptom Scale score from the Functional Assessment of Anorexia/Cachexia Therapy at 12 weeks.

Results: A total of 6,016 patients were included in the safety analysis set: 3,792 (63.0 %) were male and 2,316 (38.5 %) were aged ≧ 75 years; 4,024 patients (66.9 %) were on medication and 1,992 (33.1 %) were on best supportive care. The identified major risk factors were as follows: a history of or concomitant metabolic disease and an ECOG Performance Status of 0-1 for hyperglycemia-associated TRAEs; a concomitant hepatic disease for hepatic impairment-associated TRAEs; and a history of or concomitant cardiac disease and use of cardiotoxic antineoplastic drugs for conduction disorders-associated TRAEs. Among 4,511 patients included in the effectiveness analysis set, the following factors were identified as predictive for the effectiveness of ANA: BMI <20 kg/m^2, those who are on medication, concomitant use of platinum-containing drugs, and absence of concomitant metabolic diseases.

Conclusion: We identified putative predictive factors for TRAEs and clinical response in ANA treatment. Further investigation will be required to confirm the predictability of those factors.

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