showed continuous increase in ctDNA concentration (287.09 MTM/mL). Separate analyses indicated MSI-high and PD-L1 positive tumor status, leading to the initiation of the first line of therapy (nab-paclitaxel and Atezolizumab), which resulted in ctDNA decline (39.62 MTM/ml). Weekly ctDNA monitoring noted a rapid increase a month later (178 MTM/ml to 833.69 MTM/ml) within a 2-week interval, which corresponded to disease progression on imaging. Given non-responsiveness with the first-line therapy, the patient was initiated with sacituzumab govitecan. Following this, a rapid decline in the ctDNA level was observed within a week (364.07 MTM/mL) with a downward trend to 73.03 MTM/ml by two weeks. An interval PET/CT scan showed a mixed response. Continued monitoring of ctDNA demonstrated ctDNA levels <5MTM/mL for a period of two months before serially rising again (to 89.27 MTM/ml). PET-CT ordered in response to increasing ctDNA levels confirmed progression involving hepatic and lung lesions. A new line of therapy with nivolumab and ipilimumab was subsequently initiated.

Conclusions Serial monitoring of ctDNA enables early detection of therapy resistance and provides a rationale for treatment change/optimization/discontinuation as compared to periodic imaging that is currently the standard of care. The ease and convenience of using ctDNA-based testing as frequently as every week clearly identified earlier non-responsiveness to IO and also identified earlier acquired resistance to antibody-drug conjugate, enabling a prompt switch to alternative therapy.

Ethics Approval N/A

Consent N/A

REFERENCES

1. Anders C, Carey LA. Understanding and treating triple-negative breast cancer. *Oncology (Williston Park)*. 2008;**22**(11):1233–1243.
2. Mehanna J, Haddad FG, Eid R, Lambertini M, Kourie HR. Triple-negative breast cancer: current perspective on the evolving therapeutic landscape. *Int J Womens Health* **2019**;11:431–437. Published 2019 Jul 31. doi:10.2147/IJWH.S178349
3. Treatment of Triple-negative Breast Cancer. American Cancer Society Website. Updated 2020. Accessed August 10, 2020. https://www.cancer.org/cancer/breast-cancer/treatment/treatment-of-triple-negative.html
4. Bardia A, Mayer IA, Vahdat LT, *et al*. Sacituzumab govitecan-hziy in refractory metastatic triple-negative breast cancer. *N Engl J Med* 2019;**380**(8):741–751. doi:10.1056/NEJMoa1814213

http://dx.doi.org/10.1136/jitc-2020-SITC2020.0025

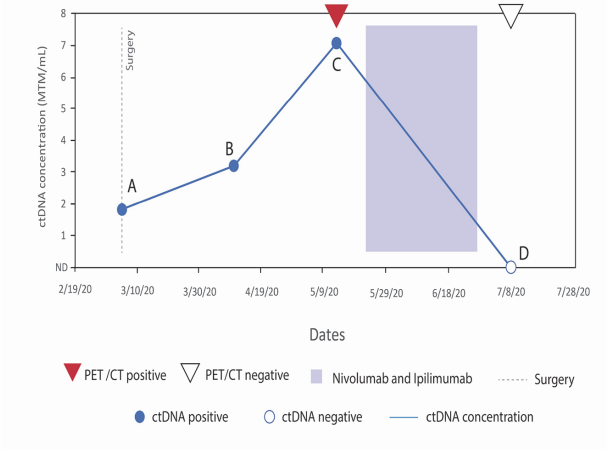
26 CTDNA CLEARANCE AND RADIOGRAPHIC RESOLUTION OF LYMPH NODE METASTASIS IN A PATIENT WITH METASTATIC MICROSATELLITE STABLE COLORECTAL CANCER ON IMMUNOTHERAPY

[1]Charles Schneider*, [2]Michael Krainock, [2]Meenakshi Malhotra, [2]Paul Billings, [2]Alexey Aleshin. [1]*University of Pennsylvania, Philadelphia, PA, USA*; [2]*Natera, Inc., San Carlos, CA, USA*

Background High microsatellite instability (MSI-H) in metastatic colorectal cancer (mCRC) is associated with a beneficial response to immunotherapy. Additionally, within MSI-H cancers, tumor mutational burden (TMB) is independently predictive of immunotherapy responsiveness.[1] Durable responses to therapy have been demonstrated in patients with MSI-H mCRC treated with Nivolumab and Ipilimumab.[2] However, less is known about treatment responsiveness in patients with high mutational burden mCRC that demonstrates microsatellite stability (MSI-L).

Methods We report on a 55-year-old female with a PALB-2 germline mutation who presented with a right-sided colonic adenocarcinoma with the involvement of the omentum and liver. The patient received 6 cycles of neoadjuvant FOLFOX, followed by an extended right hemicolectomy, omentectomy, and partial liver resection. The surgical specimen revealed a moderately differentiated adenocarcinoma in the cecum demonstrating a poor response to chemotherapy, 0/23 lymph nodes positive, one focus of adenocarcinoma in the liver with clear margins, and focal omental involvement with adenocarcinoma. The patient subsequently underwent 6 cycles of 'adjuvant' FOLFOX, with Oxaliplatin omitted after 3 cycles secondary to peripheral neuropathy. Soon after the patient experienced a recurrence that involved the anterior abdominal wall, between the peritoneum, and stomach, which was subsequently resected with negative margins. Molecular profiling of this metastatic focus revealed a TMB of 15.4 mutations per megabase, proficient Mismatch Repair (pMMR), a PDL1 CPS score of 26, and microsatellite stable (MSS) status. First, ctDNA analysis was performed at the time of recurrence and was found to be positive. Based on the TMB score of 15.4 and an elevated PDL1 score, the patient was initiated on Nivolumab and Ipilimumab. ctDNA measurements were obtained at the patient's request.

Results DNA assessment performed after surgery and prior to initiation of immunotherapy revealed an approximate doubling of ctDNA levels, measured in mean tumor molecules (MTM) per mL of plasma, every month. During this period of time and correlating with the rise in ctDNA levels, the patient developed a new and enlarging FDG avid cardiophrenic lymph node. Following 2 cycles of Nivolumab and Ipilimumab, the FDG avid lymph node completely resolved and ctDNA clearance was observed (figure 1).



Abstract 26 Figure 1 ctDNA time-course demonstrating ctDNA kinetics
Time-point A represents the initial ctDNA assay, performed at the time of resection of peritoneal metastasis. An additional time-point (B) drawn a month later reveals a further increase in ctDNA. Time-point C represents a peak in ctDNA levels, concomitant with the new emergence of a PET avid cardiophrenic lymph node. Combination Immunotherapy (IO) was begun shortly after time-point C. Time-point D represents ctDNA clearance and radiographic resolution of lymph node metastasis after two cycles of IO. MTM/mL - mean tumor molecules/milliliter of plasma

Conclusions Here we present a case of ctDNA clearance correlating with a radiographic resolution of metastatic disease in a patient with MSS mCRC. The data is provocative and suggests a possible contributory role of ctDNA-based testing as an additional monitoring parameter to measure disease-responsiveness to immunotherapy. Further investigation is warranted.
Ethics Approval N/A
Consent N/A

REFERENCES

1. Schrock AB, Ouyang C, Sandhu J, Sokol E, Jin D, Ross J8, Miller VA, Lim D, Amanam I, Chao J, Catenacci D, Cho M, Braiteh 7, Klempner SJ, Ali 8M, Fakih M. Tumor mutational burden is predictive of response to immune checkpoint inhibitors in MSI-high metastatic colorectal cancer. *Ann Oncol* 2019;**30**(7):1096–1103
2. Overman MJ, *et al*. Durable Clinical/Benefit With Nivolumab Plus Ipilimumab in DNA Mismatch Repair-Deficient/Microsatellite Instability-High Metastatic Colorectal Cancer. *Clin Oncol* 2018;**36**(8):773–779.

http://dx.doi.org/10.1136/jitc-2020-SITC2020.0026

27 THE ROLE OF LIGANDS OF ACTIVATORY RECEPTOR NKG2D IN THE IMMUNE-DEPENDENT PATHOGENESIS AND EVOLUTION OF INFLAMMATORY BOWEL DISEASE (IBD)

[1]Heba Sidahmed, [1]Shilpa Ravindran, [1]Harshitha Manjunath, [1]William Mifsud, [1]Adrian Charles, [2]Adham Ammar, [2]Muhammad Khan, [2]Saad Al-Kaabi, [1]Anthony Akobeng, [2]Muneera Al-Mohannadi, [1]Mamoun Elawad, [1]Sara Tomei, [1]Cristina Maccalli*. *[1]Sidra Medicine, Doha, Qatar; [2]Hamad Medical Corporation, Doha, Qatar*

Background Long-term inflammation in IBD is mediated by several immune cells, including T lymphocytes and natural killer (NK) cells, through the engagement of NK group 2D (NKG2D) receptors. Allelic variations of NKG2D ligands (NKG2Dls, MICA/B, ULBP1-3) influence differential levels and localization of protein expression or the release of soluble isoforms. The affinity of interaction with NKG2D can be also affected, modulating the cytotoxic activity of the target cell. Evaluation of these molecular pathways and soluble ligands presents the potential use a clinical biomarker for patient outcomes.
Methods Gut tissue biopsies (left and right sides) and peripheral blood were collected from patients. 10 pediatric and 11 adult patients with IBD, 10 patients with gut malignancies and history of IBD were included in the study. Plasma form IBD patients and 10 healthy donors as controls, was used to quantify soluble NKG2DLs (sNKG2DLs) by ELISA (R&D Systems Duo Set). Nucleic acids were extracted from gut biopsies using the BioMasher II (Kimble) and All Prep DNA/RNA universal kit (Qiagen). Single nucleotide polymorphisms (SNPs, N=26) and relative gene expression of NKG2DL genes were conducted by qPCR using Taqman assays.
Results 9/11 adult patients had diagnosis of ulcerative colitis, compared to 3/10 pediatrics. 5/10 pediatrics had Crohn's disease and 2/10 unclassified IBD. A trend of prevalence of some allelic variants was detected for most of NKGD2Ls.In addition, mRNA encoding for NKG2DLs was detected commonly, although with heterogeneous quantifications, in all the tissues, including the retrospectively collected malignancies with history of IBD. Interestingly, the levels of sNKG2DLs were higher in pediatric ($p<0.001$) as compared to adult patients. No or low levels of sNKG2DLs were detectable in healthy donors. Moreover 3/5 patients with the highest level (700–1500 pg/ml) of sMICA had homozygosity at least in one of the rs1051792 or rs1051794 polymorphic site (GG allele variant MICA-129Val or MICA-250Val) that have been reported to be associated with soluble form of MICA.
Conclusions These results, although preliminary and further investigations are ongoing, suggest the relevance of NKG2D/NKG2DL pathway in the development and evolution of IBD. sNKG2DLs could be detected in most of patients, with different levels and highest concentrations in pediatric patients. In some cases, the presence of sNKG2DLs in the plasma could be associated with defined polymorphisms in genes encoding for these proteins.
Ethics Approval This study was approved by Sidra Medicine and Hamad Medical Corporation Ethics Boards; approval number 180402817 and MRC-02-18-096, respectively.

http://dx.doi.org/10.1136/jitc-2020-SITC2020.0027

28 RETROSPECTIVE POOLED ANALYSIS OF EPACADOSTAT CLINICAL STUDIES IDENTIFIES DOSES REQUIRED FOR MAXIMAL PHARMACODYNAMIC EFFECT IN ANTI-PD-1 COMBINATION STUDIES

Michael Smith*, Robert Newton, Sherry Owens, Xiaohua Gong, Chuan Tian, Janet Maleski, Lance Leopold. *Incyte Corporation, Wilmington, DE, USA*

Background IDO1 is the initial rate-limiting enzyme in one breakdown pathway of tryptophan. It reduces tryptophan levels and generates metabolites (e.g., kynurenine [KYN]) that contribute to tumor-associated immune suppression. Epacadostat (EPA) is a novel, potent, selective, reversible inhibitor of IDO1 studied in clinical trials in combination with anti-PD-1 antibodies. Epacadostat-induced decreases in plasma KYN have been used as a pharmacodynamic measure of drug activity and have aided in dose selection for clinical studies. Despite encouraging signs of efficacy in combination with pembrolizumab (PMB) in the ECHO-202 study, a large phase 3 study in melanoma (ECHO-301) failed to reproduce this outcome.[1]
Methods Longitudinal plasma samples were obtained from participants in EPA clinical studies. Plasma KYN and EPA concentrations were measured by validated liquid chromatography tandem mass spectrometry. Quantitative mass spectrometry imaging (qMSI) of intratumoral tryptophan metabolites was also performed.
Results Analysis of plasma KYN levels demonstrated that PMB monotherapy significantly elevated KYN. While blocking the PMB-induced increase, EPA (100 mg BID) in combination with PMB failed to normalize KYN to healthy control levels as was reported for EPA monotherapy.[2] Because anti-PD-1 treatment can induce interferon gamma (IFN-γ) production and IDO1 expression is IFNg inducible,[3] we hypothesize that PMB-induced IFN-γ may be responsible for the observed increase of plasma KYN levels. Combined analysis of plasma KYN from additional EPA/anti-PD-1 combination (ECHO-202; EPA/PMB, ECHO-204; EPA/nivolumab) and monotherapy (ECHO-210) studies, with EPA doses ranging from 50 to 600 mg BID, suggested that higher EPA doses (≥600 mg BID) may be necessary to overcome the anti-PD-1–associated KYN elevation. Doses ≥600 mg BID are projected to cover the EPA IC90 value for 24h. The POD1UM-102 study is currently evaluating the combination of a novel anti-PD-1 monoclonal antibody (retifanlimab) plus EPA at doses up to 900 mg BID. Preliminary results from this study indicate that 600 mg BID is the maximally tolerated dose and is capable of maintaining suppression of KYN to healthy control levels through treatment cycle 4. Additionally, qMSI of paired