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MEETING SUMMARY
UPDATE FROM ENETS 2019
Barcelona, Spain

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BIO-MARKERS IN NENs

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BIOMARKERS IN NENs

REVIEW OF DATA FROM ENETS 2019

NENs, neuroendocrine neoplasms

BACKGROUND

- Some biomarkers are currently available for functioning and non-functioning NENs
- Currently utilised **monoanalyte biomarkers** (e.g. chromogranin A, serotonin, pancreastatin etc.) exhibit variable metrics, **insufficient** sensitivity, specificity, and **predictive ability**
- No single (monoanalyte) biomarker has proven to be effective and there remains an **unmet need for novel biomarkers to improve diagnosis and predict patient outcome**
- **Several novel biomarkers are being evaluated** and may become future tools for the management of NENs. These include:-
  - peptides and growth factors
  - DNA and RNA markers based on genomics analysis (e.g. NETest)
  - circulating tumor/endothelial/progenitor cells or cell-free tumor DNA
  - imaging techniques with novel radiolabeled somatostatin analogs or peptides

NENs, Neuroendocrine Neoplasms; NETest, neuroendocrine neoplasms test

Herrera-Martinez, AD. Endocrine-Related Cancer 2019; 26: R157-R179; Modlin, IM. Best Practice & Research Clinical Endocrinology & Metabolism, 2016; 30: 59-77

MONOANALYTE CLASSIC BIOMARKERS IN NET

Monoanalyte classic biomarkers in NET correlate with the disease course and clinical symptoms, and may have prognostic value and predict response to treatment

Circulating markers

- Chromogranin A, Neuron specific enolase, Pancreatic polypeptide, 5-HIAA, Gastrin, Glucagon etc

Tissue markers

- NENs differentiation, proliferation (Ki-67)

Imaging markers

- Anatomical imaging (CT, MRI), functional imaging (SRS, FDG PET/CT) etc

CT, computerised tomography; FDG, fluorodeoxyglucose; 5-HIAA, 5-hydroxyindoleacetic acid; MRI, magnetic resonance imaging; NEN, Neuroendocrine neoplasm; PET, positron emission tomography; SRS, Stimulated Raman spectroscopy

1. Scarpa A, et al. Nature. 2017; 543:65-71; 2. Nunez-Valdovinos B, et al. The Oncologist 2018; 422-432; 3. Childs A, et al. Endocr Relat Cancer 2016; 23(7):563-570; 4. Faivre S, et al. Target Oncol 2012, 7: 127-133

MULTIANALYTE NOVEL BIOMARKERS IN NET

Multianalyte novel biomarkers in NET may reflect better NENs complexity and heterogeneity. They may also be useful in predicting disease progression and treatment efficacy

Circulating biomarkers

- NETest , CTC, MGMT, SMAD2/4 expression, c-KIT, VEGF, sVEGFR2-3, IL-8 etc.

Theranostics and radiomics

- Functional imaging techniques using SSTR PET using SSTR-agonists or antagonists
- PET imaging of dopamine transport system using F-18 DOPA (Fluorodopa)
- PET imaging of tumour glycolytic activity using F-18 FDG (Fluorodeoxyglucose)
- dual tracer PET/CT
- Total body PET/CT scanner – the 'EXPLORER' , etc.

CT, computerised tomography ; CTC, circulating tumour cells; IL-8, interleukin 8; MGMT, O6-methylguanine DNA methyltransferase; NETest, neuroendocrine neoplasms test; PET, positron emission tomography; SSTR, somatostatin receptor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor

1. Yao JC, et al. J Clin Onco. 2016; 34(32): 3906-3913; 2. Basu B, et al. Cancer Biother Radiopharm 2016;31(3):75-84; 3. Bi WL, et al. CA Cancer J Clin 2019; 69:127-157; 4. Hofland J, et al. Nat Rev Endocrinology 2018; 14(11):656-669; 5. Liu E, et al. The Oncologist 2018; doi: 10.1634/theoncologist.2017-0623; 6. Bodei L, et al. Eur J Nucl Med Mol Imaging 2016; 43(5):839-851

CIRCULATING BIOMARKERS

POSTER HIGHLIGHTS FROM ENETS 2019

- A number of studies validated the NETest as a marker of disease progression and treatment efficacy
  - **NETest blood levels** were found to **effectively monitor PRRT efficacy** with a decrease in NETest blood levels from pre-PRRT correlating to a significantly longer PFS[1]
  - **Elevated NETest** was found to be diagnostic of BPC with levels **accurately identifying progression** as determined by RECIST[2]
  - **Elevated NETest correlated** consistently with residual and/or **progressive disease** in patients with midgut NETs post resection[3]

BPC, bronchopulmonary carcinoids; NET, neuroendocrine tumour; NETest, neuroendocrine neoplasms test; PFS, progression free survival; PRRT, peptide receptor radionuclide therapy; RECIST, response evaluation criteria in solid tumours

1. Bodei L, et al. ENETS 2019, abstract F04; 2. Malczewska A et al. ENETS 2019, abstract F19; 3. Laskaratos F et al. ENETS 2019, abstract F14

CIRCULATING BIOMARKERS

POSTER HIGHLIGHTS FROM ENETS 2019

- A study investigated the expression of SSTR2 and MGMT in various NENs
  - Both **SSTR2 and MGMT** were **strongly linked to treatment response** and therefore can predict prognosis and guide treatment decisions for different NENs

MGMT, O6-methylguanine DNA methyltransferase; NEN, neuroendocrine neoplasm; SSTR, somatostatin receptor

Liu z, et al. ENETS 2019, abstract F17

THERANOSTICS AND RADIOMICS MARKERS

POSTER HIGHLIGHTS FROM ENETS 2019

- A study identified **32 stable and unique features in 68Ga-DOTATATE PET** for radiomics research. Further evaluation of these features is required to determine their prognostic and predictive value of therapy response and survival in NET[1]

- FDG MTV and TLG were investigated as NEN biomarkers. Results found that quantitative analysis of FDG PET in NEN is feasible and **high MTV/TLG are predictors of poor prognosis in NEN**[2]

FDG, 18-fluorodeoxyglucose; MTV, metabolic tumour volume; NEN, neuroendocrine neoplasm; NET, neuroendocrine tumour; PET, positron emission tomography; TLG, total lesion glycolysis

1. Aalbersberg E, et al. ENETS 2019, abstract K01; 2. Chan D, et al. ENETS 2019, abstract K08

THERANOSTICS AND RADIOMICS MARKERS

POSTER HIGHLIGHTS FROM ENETS 2019

- A quantitative lesion based analysis of the role of FDG and DOTATATE PET in predicting PRRT efficacy was conducted. Results showed **FDG PET metrics did not predict PRRT efficacy**, however **DOTATATE SUVmax did**[1]

- A study investigated the prognostic value of combined Ga-DOTATATE/FDG PET imaging compared to Ki-67 grading in patients with metastatic GEP-NENs. Combined **Ga-DOTATATE/FDG PET imaging significantly improved prognostic stratification in patients with metastatic GEP-NENs**[2]

FDG, 18-fluorodeoxyglucose; NEN, neuroendocrine neoplasm; PET, positron emission tomography; PRRT, peptide receptor radionuclide Therapy; SUV, standardised uptake values

1. Chan D, et al. ENETS 2019, abstract K09; 2. Karfis I, et al. ENETS 2019, abstract K20

SUMMARY

- There are currently **few predictive biomarkers** in NET and in the future these may become **part of routine clinical practice**
- **Several ongoing prospective trials** evaluating the effect of novel therapeutic strategies in NENs and most **include the evaluation of treatment-related follow-up markers**
- **Circulating markers**, as well as non-invasive techniques for early diagnosis would be **valuable to identify a personalized therapeutic sequence and follow-up**
- **Combination of markers** that **better predict the course of the disease**, would allow for **better decision making** with regard to available treatment options

NEN, neuroendocrine neoplasms; NET, neuroendocrine tumours

Couvelard, A. Summary of oral presentation at ENETS 2019; Herrera-Martinez, AD. Endocrine-Related Cancer 2019; 26: R157-R179

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