Gastric Cancer: Molecular Classifications

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1. PAST MEDICAL HISTORY:

➢ 43 year-old man with longstanding hyperglycemia and obstructive sleep apnea as main comorbidities.

2. ONCOLOGY HISTORY:

➢ Diagnosis: FGS and CT scan confirmed a stage IV antral diffuse adenocarcinoma HER2 positive (IH 2+, ISH amplified), EBV positive (EBER-ISH), MSS.

Gastric Cancer ESMO Clinical Practice Guidelines _Ann Oncol_ vol 27; suppl 5 Sept 2016, pp.v38-v49.
First palliative line:

Patient received first palliative line within the JACOB trial (NCT01774786), receiving 6 cycles of cisplatin/capecitabine/trastuzumab/pertuzumab or placebo.

Partial response was achieved as best response, and he continued then with capecitabine/trastuzumab/pertuzumab or placebo maintenance until May’ 15 (PFS of 9 months).

STOP as per progressive disease.
Second palliative line:

He received second palliative line with paclitaxel/ramucirumab 11 cycles, with partial response as best response (PFS of 11 months).

However, he progressed with new bone metastases and lymph nodes, for which he was then referred for considering phase 1 trial options in the refractory setting.

➢ Third palliative line:

In light that he was EBV+, he received nivolumab within an early clinical trial, from Oct-Dec 2016, with *progressive disease as best response*.

➢ Fourth palliative line:

In light that he was HER2+, he received a bi-specific antibody targeting dual blockade of HER2/HER3 within an early clinical trial, from Jan-Feb 2017, with *progressive disease as best response*.

➢ Fifth palliative line:

He received **CPT-11**, from Feb-June 2017, with *clinical benefit with radiological stabilization as best response*.

Patient died on July 2017 due to progressive disease.
3. RATIONALE FOR MOLECULARLY-GUIDED THERAPIES in GC PATIENTS:

- GC/GOJ cancer is an heterogeneous disease.

TCGA GC_ Nature 2014; 11th September, 513: 202-209
4. DIFFERENT MOLECULAR CLASSIFICATIONS IN GC:

A comprehensive survey of genomic alterations in gastric cancer reveals systematic patterns of molecular exclusivity and co-occurrence among distinct therapeutic targets.

ARTICLE
Comprehensive molecular characterization of gastric adenocarcinoma

Molecular analysis of gastric cancer identifies subtypes associated with distinct clinical outcomes.

2012\(^1\)  2013\(^2\)  2014\(^3\)  2015\(^4\)

5. HETEROGENEOUS GENE EXPRESSION IN GC:

➢ Co-occurrence of molecular alterations has been described.

➢ Should we re-define which molecular alteration is the driver in a specific patient? Maybe addressing only one of the biomarkers is not enough...

6. WHAT DOES THE FUTURE HOLD FOR GASTRIC CANCER PATIENTS?

48 year-old patient with metastatic GC adenocarcinoma HER2+/EBV+/MSS who underwent 5 different oncological treatments:

➢ Improved PFS first line 9 months (reported 6.7 months for HER2+ CDDP/5FU/trastuzumab; Bang Y et al. *Lancet* 2010 Aug 28;376(9742):687-97).

➢ Improved PFS second line 11 months (reported 4.4 months for paclitaxel/ramucirumab; Wilke HH. et al. *Lancet Oncol* 2014;15:1224-35).

Remarkably, he achieved response with trastuzumab and ramucirumab, but progressed through immunotherapy (CIN versus GS versus EBV subtype).

➢ Need for consensus molecular subtype classification and personalized strategies.

➢ Re-define evaluation of predictive biomarkers (HER2/EBV positivity criteria and others).

➢ Improvements in clinical trial design, with incorporation of validated predictive biomarkers.

➢ Real inclusion/exclusion criteria adapted to the GC population to be treated.
Thank you!