MSI, HRD and liquid biopsy in esophago-gastric cancer and other digestive tumors

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- Speaking: MSD, BMS, Lilly, Roche, Amgen
• MSI, HRD and liquid biopsy in esophago-gastric cancer and other digestive tumors

• MSI → gastric and colon cancer
• HRD → gastric and pancreatic cancer
• Liquid biopsy → gastric and colon cancer

• Conclusions
Outline

• **MSI, HRD and liquid biopsy in esophago-gastric cancer and other digestive tumors**

• **MSI** → gastric and colon cancer
  - **HRD** → gastric and pancreatic cancer
  - **Liquid biopsy** → gastric and colon cancer

• Conclusions
Molecular subtypes of esophago-gastric cancer
2nd Line Treatment of GC

KEYNOTE 061 (Phase III)

OS, ORR, and DOR for MSI-H Tumors

Event/Pts
Pembrolizumab: 6/15, HR 0.42 (95% CI 0.13-1.31)
Paclitaxel: 10/12

Medians (95% CI)
Pembrolizumab: OS NR (5.6 mo-NR)
Paclitaxel: OS 8.1 mo (2.0-16.7)

CR: 46.7%
PR: 16.7%

No. at risk
Pembrolizumab: 15, 12, 11, 6, 3, 1, 0, 0
Paclitaxel: 12, 8, 8, 3, 1, 0, 0

DOR, mo (median [range])
Pembrolizumab: (5.5 to 26.0+)
Paclitaxel: (2.2+ to 12.2+)

>2\textsuperscript{nd} Line Treatment of GC

KEYNOTE 059 Cohort 1 – MSI-H GC (Phase II)

<table>
<thead>
<tr>
<th>Response\textsuperscript{a}</th>
<th>MSI-High (n = 7)</th>
<th>Non-MSI-High (n = 167)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>95% CI</td>
</tr>
<tr>
<td>ORR</td>
<td>57.1</td>
<td>18.4-90.1</td>
</tr>
<tr>
<td>CR</td>
<td>14.3</td>
<td>0.4-57.9</td>
</tr>
<tr>
<td>PR</td>
<td>42.9</td>
<td>9.9-81.6</td>
</tr>
<tr>
<td>DCR\textsuperscript{b}</td>
<td>71.4</td>
<td>29.0-96.3</td>
</tr>
</tbody>
</table>
The MSI-H patient who did not respond had an heterogenic tumor with MSI and MSS areas.
CMS subtypes of CRC

CMS1
- MSI - Immune 14%
  - Immune
    - Microsatellite instability
    - CIMP high
    - Hypermutation, *BRAF* mutations
    - Immune activation

CMS2
- Canonical 37%
  - Epithelial A
    - High chromosomal instability
    - Microsatellite stable
    - CIMP negative
    - WNT and MYC activation

CMS3
- Metabolic 13%
  - Epithelial B
    - Heterogeneous chromosomal/microsatellite status
    - *KRAS* mutations
    - Metabolic reprogramming

CMS4
- Mesenchymal 23%
  - Mesenchymal
    - High chromosomal instability
    - TGFβ activation
    - Invasion, matrix remodeling
    - Angiogenesis

MSI-H vs MSS in CRC

KEYNOTE 016

Adapted from TCGA Nature 2012 and Le NEJM 2015
MSI refractory MSI-H CRC

KEYNOTE 164 (Phase II)

MSI mCRC patients presented 32% RR regardless number of prior lines

76% of patients alive 1 year after starting therapy
CheckMate 142 Study Design

- CheckMate 142 is an ongoing, multi-cohort, nonrandomized phase 2 study evaluating the efficacy and safety of nivolumab-based therapies in patients with mCRC (NCT02060188).
- Cohorts 1 & 2
  - MSI-H/dMMR per local laboratory
  - Histologically confirmed metastatic or recurrent CRC
  - Previously treated
  - NIVO3 Q2WP
  - NIVO3 + IP1 Q3W (4 doses and then NIVO3 Q2WP)
  - Primary endpoint: ORR per investigator assessment (RECORD v1.1)
  - Other key endpoints:
    - ORR per BICR, DCR, DoR, PFS, OS, and safety
- Median follow-up for the 1L nivolumab plus low-dose ipilimumab cohort was 13.8 months (range, 9–19).

Investigator-Assessed Response and Disease Control

- Nivolumab + ipilimumab: ORR (95% CI): 51.3% (45.2, 58.3)
- Nivolumab: ORR (95% CI): 31% (20.8, 42.9)
- DCR was 80% (95% CI: 71.5, 86.6) with combination therapy and 69% (67.1, 79.2) with monotherapy.
- Combination therapy provided a numerically higher ORR, including CRs, and DCR relative to monotherapy during a similar follow-up period.

Progression Free and Overall Survival

- 9-month rate (95% CI), %: Nivolumab + ipilimumab 70 (67.0, 72.7), Nivolumab 54 (41.5, 64.5)
- 12-month rate (95% CI), %: Nivolumab + ipilimumab 71 (61.4, 78.7), Nivolumab 50 (38.1, 61.4)
- With similar follow-up, combination therapy provided improved PFS and OS relative to monotherapy.

CheckMate 142 Study Design

- CheckMate 142 is an ongoing, multi-cohort, nonrandomized phase 2 study evaluating the efficacy and safety of nivolumab-based therapies in patients with mCRC (NCT02060188)
- Previously treated
- MSI-H/dMMR per local laboratory
- Median follow-up for the 1L nivolumab plus low-dose ipilimumab cohort was 13.8 months (range, 9–19) [c]

Primary endpoint:
- ORR per investigator assessment (RECIST v1.1)

Other key endpoints:
- ORR per BICR, DCR, DOR, PFS, OS, and safety

Best Reduction in Target Lesions

84% of patients had a reduction in tumor burden from baseline

Progression-Free and Overall Survival

MSI-H first line CRC

Cohorts 1 & 2

Cohort 3

Lenz ESMO 2018
DNA Mismatch Repair System and biologic importance of Microsatellites

- **Microsatellites** are repetitive DNA sequences with a unit length ranging from one to six bases distributed along **coding** and **noncoding** regions of the genome.
  - Highly polymorphic among subjects, stable in each individual
- **DNA Mismatch repair** is a highly conserved mechanism involved in restoring DNA integrity after the occurrence of mismatching errors
- **Four genes** regulate the MMR mechanism - mutL homologue 1 (**MLH1**), mutS homologue 2 (**MSH2**), mutS homologue 6 (**MSH6**) and postmeiotic segregation increased 2 (**PMS2**)

Vilar & Gruber Nat Rev Clin Oncol 2010
MSI Testing

MSS Tumor

MSI Tumor
How to assess MSI

- The MSI status doesn’t change in the time
- Although historically it has been tested in tumor, there are new proposals in liquid biopsy
<table>
<thead>
<tr>
<th>Line</th>
<th>Study</th>
<th>Treatment Arms</th>
<th>Ph</th>
<th>Line</th>
<th>Treatment</th>
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<tr>
<td></td>
<td>CHECKMATE 649</td>
<td>Ipilimumab + Nivolumab XELOX Nivolumab XELOX</td>
<td>III</td>
<td>1st Line MSI CRC</td>
<td>Ipilimumab + Nivolumab XELOX Nivolumab XELOX</td>
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<tr>
<td></td>
<td>KEYNOTE 859</td>
<td>XELOX Pembrolizumab XELOX Placebo</td>
<td>III</td>
<td>1st Line MSI CRC</td>
<td>Pembrolizumab XELOX Placebo</td>
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<td>KEYNOTE 811</td>
<td>CISPLATIN – CPC Pembrolizumab CISPLATIN – CPC Placebo</td>
<td>III</td>
<td>1st Line MSI CRC</td>
<td>Pembrolizumab CISPLATIN – CPC Placebo</td>
</tr>
<tr>
<td></td>
<td>JAVELIN Gastric 100</td>
<td>FOLFOX/XELOX x12 weeks, thereafter: Avelumab 10mg/kg Q2W Continuation FOLFOX/XELOX</td>
<td>III</td>
<td>1st Line MSI CRC</td>
<td>Pembrolizumab XELOX Placebo</td>
</tr>
<tr>
<td>Mainten ance</td>
<td>MAGEC</td>
<td>Atezolizumab + different Ab Paclitaxel-ramucirumab</td>
<td>III</td>
<td>1st Line MSI CRC</td>
<td>Pembrolizumab XELOX Placebo</td>
</tr>
<tr>
<td>2nd Line</td>
<td>MAGEC</td>
<td>Atezolizumab + different Ab Paclitaxel-ramucirumab</td>
<td>III</td>
<td>Adjuvancy Stage III MSI CRC</td>
<td>Pembrolizumab XELOX Placebo</td>
</tr>
</tbody>
</table>

Ongoing trials in gastric and colon cancer

- **KEYNOTE-177** III 1st Line MSI CRC Pembrolizumab vs FOLFOX-Bv
- **NCT02997228** III 1st Line MSI CRC FOLFOX + Bv vs. FOLFOX-Bv-Atezo vs. Bv-atezo
- **Checkmate 142** III Cohort 3: 1st Line MSI CRC (OS, PFS) Pembrolizumab vs Nivolumab
  - Cohort 5: Refractory MSI CRC Pembrolizumab vs Nivolumab + anti-LAG3
- **NTC02912559** III Adjuvancy Stage III MSI CRC Pembrolizumab +/- Atezolizumab
Outline

• MSI, HRD and liquid biopsy in esophago-gastric cancer and other digestive tumors
  • MSI → gastric and colon cancer
  • HRD → gastric and pancreatic cancer
  • Liquid biopsy → gastric and colon cancer

• Conclusions
Synthetic lethal targeting of BRCA mutant tumors with PARP inhibitors

- *BRCA1* and *BRCA2* are tumor suppressor genes and germline mutations are associated with elevated breast, ovarian, prostate and pancreatic cancer risk.

- *BRCA1/2* encode key components of the homologous recombination repair pathway.

- Rationale for targeted therapy in *BRCA*-mutated tumors based on pre-clinical demonstration of synthetic lethality with PARP inhibitors.

![Diagram](Soonenblick Nat Rev Clin Oncol 2015)
Landscape of BRCA 1/2 MT and gLOH across cancer types

Although the highest frequency of BRCA1/2 alterations and gLOH-H is found in ovarian and breast cancer, it is also present in biliary tract and esophago-gastric cancer.
• Determination of whether an alteration is heterozygous vs homozygous/bi-allelic is important
  – Homozygous/bi-allelic BRCA alterations are associated with increased gLOH-H in most cancer types
  – Heterozygous BRCA = wild-type gLOH score
• Concurrent assessment of homozygous/bi-allelic and heterozygous status of BRCA status may be necessary as a potential biomarker for PARP inhibition
Olaparib in combination with paclitaxel in patients with advanced gastric cancer who have progressed following first-line therapy (GOLD): a double-blind, randomised, placebo-controlled, phase 3 trial

Yung-Jue Bang, Rui-Hua Xu, Keisha Chin, Keun Wook Lee, Se Hoon Park, Sun Young Rha, Lin Shen, Shukui Qin, Nong Xu, Seock Ah Im, Gershon Locker, Phil Rowe, Xiaojun Shi, Darren Hodgson, Yu-Zhen Liu, Norikazu Boku

- Phase III trial, 525 GC patients
- Olaparib 100 mg BID daily plus paclitaxel 80 mg/m2

OS in the Overall Population

OS in the ATM-neg (18%)
10% of PC are found within a familiar clustering
- In these, prevalence of BRCA MT ≈ 17%
Olaparib Monotherapy in Patients With Advanced Cancer and a Germline BRCA1/2 Mutation


- Phase II trial
- BRCA 1/2 germline mutated tumors
- Olaparib monotherapy 400mg BID

- In PC patients:
  - ORR ≈ 22%
  - mOS 9.8 months
## Ongoing trials with PARP inhibitors in PC

<table>
<thead>
<tr>
<th>Treatment/Line</th>
<th>Ph</th>
<th>Alteration</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olaparib maintenance</td>
<td>3</td>
<td>BRCA 1 or 2 germline mutations</td>
<td>NCT02184195</td>
</tr>
<tr>
<td>Rucaparib maintenance</td>
<td>2</td>
<td>BRCA 1/2 and PALB2 germline mutations</td>
<td>NCT03140670</td>
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<tr>
<td>Olaparib</td>
<td>2</td>
<td>BRCAness signature</td>
<td>NCT02677038</td>
</tr>
<tr>
<td>FOLFIRI + veliparib</td>
<td>2</td>
<td>Unselected</td>
<td>NCT02890355</td>
</tr>
</tbody>
</table>
Outline

• MSI, HRD and liquid biopsy in esophago-gastric cancer and other digestive tumors

• MSI $\rightarrow$ gastric and colon cancer
• HRD $\rightarrow$ gastric and pancreatic cancer
• **Liquid biopsy** $\rightarrow$ gastric and colon cancer

• Conclusions
Liquid biopsy

- Clinical application of the liquid biopsies (ctDNA and CTCs):
  - Tumor genotyping
  - Tracking the minimal residual disease
  - Assessment of drug response
  - Monitor the clonal evolution
Tumor genotyping: capture of the molecular heterogeneity

- In contrast to single tissue biopsies, blood would carry DNA derived from cancer cells located at distinct metastatic sites.
Tumor genotyping: capture of the molecular heterogeneity

<table>
<thead>
<tr>
<th>Tumor tissue RAS result</th>
<th>Plasma ctDNA RAS result</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAS</td>
<td>Mutant</td>
</tr>
<tr>
<td>Mutant</td>
<td>47</td>
</tr>
<tr>
<td>WT</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>52</td>
</tr>
</tbody>
</table>

98 mCRC
PRC in tissue; BEAMing in plasma
Overall concordance 91.8%

146 mCRC
PCR in tissue; BEAMing in tissue/plasma
Overall concordance 91.8%

115 mCRC
PCR in tissue; OncoBEAM in plasma
Overall concordance 93%
Detection of minimal residual disease

- ctDNA anticipates clinical recurrence in stage II colon cancer
Assessment of drug response and clonal evolution

Gastric Cancer

• From 24 HER2 + patients treated with TTZ:

• Patients with innate TTZ resistance showed high HER2 SCNA, PIK3A mutations, ERBB2/4 mutations

• Patients that acquire TTZ resistant during the treatment
  • Decrease HER2 SCNA levels
  • Acquire de novo NF1 mutations
Assessment of drug response and clonal evolution

Colon Cancer

Baseline analysis

Longitudinal analysis


Survival curve of mCRC patients monitored by liquid biopsy

- continued cDNA wt status
- cDNA acquired mutation
- cDNA mutation explosion
- BRAF somatic mutation

Tumor load (% of baseline)

Percentage responsive

Time (months)

0 5 10 15 20 25

0% 20% 40% 60% 80% 100%

cDNA plasma

Survival

0 10 20 30

0% 20% 40% 60% 80% 100%

Percent survival

0 20 40 60 80 100

Months
Assessment of drug response and clonal evolution

Colon Cancer

- Phase II trial, randomized (254 patients)
- Comparison of 2 regimens of Sym004 with investigator’s choice
- WT KRAS-exon2 mCRC with acquired EGFR resistance
- Sym004 did not improve OS in this unselected population

Baseline ctDNA analysis identified:
- High intrapatient genomic heterogeneity
- The acquired resistance mechanism to the anti-EGFR therapy
- A subset of patients that really could respond to Sym004
• MSI, HRD and liquid biopsy in esophago-gastric cancer and other digestive tumors

• MSI → gastric and colon cancer
• HRD → gastric and pancreatic cancer
• Liquid biopsy → gastric and colon cancer

• Conclusions
Conclusions

• **MSI** → gastric and colon cancer
  • MSI should be determined in All patients
  • In GC, not only MSI but also other biomarkers (EBV, PDL1)

• **HRD** → gastric and pancreatic cancer
  • Assessment of homozygous/bi-allelic and heterozygous status of *BRCA* status will be necessary for PARP inhibition
  • Negative results in GC, but promising in PC

• **Liquid biopsy** → gastric and colon cancer
  • Potential usefulness for tumor genotyping (overcome the tumor heterogeneity), for minimal residual disease tracking and for drug response/clonal evolution assessment
  • Prospective clinical trials are needed to validate its utility
¡MUCHAS GRACIAS!
malsina@vhio.net
Back-up slides
Nivolumab in refractory GC/GEJC (ATTRACTION-02 Phase III)

Overall Survival

Median follow-up\(^a\): 15.7 months

<table>
<thead>
<tr>
<th></th>
<th>Median OS, months (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab (N = 330)</td>
<td>5.3 (4.6–6.4)</td>
</tr>
<tr>
<td>Placebo (N = 163)</td>
<td>4.1 (3.4–4.9)</td>
</tr>
</tbody>
</table>

Hazard ratio, 0.62 (95% CI, 0.50–0.76)

\( P < 0.0001 \)

No. at Risk

\(^a\)Time from first dose to data cut-off for surviving patients

Kang YK et al. Lancet 2017
Pembrolizumab in 2nd Line GC/GEJC (Keynote 061 Phase III)

Overall Survival, CPS ≥1

<table>
<thead>
<tr>
<th>Events</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab</td>
<td>151</td>
<td>0.82 (0.65-1.03)</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>175</td>
<td></td>
</tr>
</tbody>
</table>

Median (95% CI)
- Pembrolizumab: 9.1 mo (5.2-10.7)
- Paclitaxel: 8.3 mo (7.6-9.0)

No. at risk
- Pembrolizumab: 196 130 54 23 7 0
- Paclitaxel: 199 114 78 39 14 0

CPS ≥10

Events/Pts: 34/53, 46/55
HR (95% CI): 0.64 (0.41-1.02)

Median (95% CI)
- Pembrolizumab: 10.4 mo (5.9-17.3)
- Paclitaxel: 8.0 mo (5.1-9.9)

No. at risk
- Pembrolizumab: 53 34 24 13 6 0
- Paclitaxel: 55 33 13 7 4 0

Shitara ASCO 2018; Shitara The Lancet 2018
MSI in refractory CRC

Checkmate 142 (Phase II; non-randomized)

- Histologically confirmed metastatic or recurrent CRC
- dMMR/MSI-H per local laboratory
- ≥ 1 prior line of therapy

Primary endpoint:
- ORR per investigator assessment (RECIST v1.1)

Other key endpoints:
- ORR per BICR, DCR, DOR, PFS, OS, and safety

- Median follow-up in the combination therapy cohort (N = 119) was 13.4 months (range, 9–25)\(^c\)
- Results of the monotherapy cohort (N = 74) with a similar median follow-up of 13.4 months (range, 10–32) are also presented\(^1,c\)

\(^a\)Enrollment was staggered with additional patients being enrolled if ≥ 7 of the first 19 centrally confirmed MSI-H patients had a confirmed response (CR or PR). CheckMate-142 monotherapy and combination therapy cohorts were not randomized or designed for a formal comparison. \(^b\)Patients with a CR, PR, or SD for ≥12 weeks. \(^c\)Defined here as the time from first dose to data cutoff.

Investigator-Assessed Response and Disease Control

- **DCR** was 80% (95% CI: 71.5, 86.6) with combination therapy and 69% (57.1, 79.2) with monotherapy.\(^d\)
- Combination therapy provided a numerically higher ORR, including CRs, and DCR relative to monotherapy during a similar follow-up period.\(^d\)

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\(^a\)Median follow-up was 13.4 months (range, 9–25). \(^b\)Disease control was defined as patients with a CR, PR, or SD for ≥12 weeks. \(^c\)Median follow-up was 13.4 months (range, 10–32). \(^d\)CheckMate-142 monotherapy and combination therapy cohorts were not randomized or designed for a formal comparison.

Progression Free and Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab + ipilimumab&lt;sup&gt;a,b&lt;/sup&gt;</th>
<th>Nivolumab&lt;sup&gt;1,e,f&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>9-month rate (95% CI), %</td>
<td>76 (67.0, 82.7)</td>
<td>54 (41.5, 64.5)</td>
</tr>
<tr>
<td>12-month rate (95% CI), %</td>
<td>71 (61.4, 78.7)</td>
<td>50 (38.1, 61.4)</td>
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<th>Nivolumab&lt;sup&gt;1,e,f&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>9-month rate (95% CI), %</td>
<td>87 (80.0, 92.2)</td>
<td>78 (66.2, 85.7)</td>
</tr>
<tr>
<td>12-month rate (95% CI), %</td>
<td>85 (77.0, 90.2)</td>
<td>73 (61.5, 82.1)</td>
</tr>
</tbody>
</table>

- With similar follow-up, combination therapy provided improved PFS and OS relative to monotherapy<sup>a,e,f</sup>

<sup>a</sup>Median follow-up was 13.4 months (range, 9–25).<sup>b</sup>Median PFS was not reached (95% CI, not estimable).<sup>c</sup>PFS per investigator assessment. <sup>d</sup>Median OS was not reached (95% CI, 18.0, not estimable). <sup>e</sup>Median follow-up was 13.4 months (range, 10–32).<sup>f</sup>CheckMate-142 monotherapy and combination therapy cohorts were not randomized or designed for a formal comparison.

• Refractory mCRC
• No known MSI tumors (but confirmation is ongoing)
• mOS 6.6 mo for D+T and 4.1 mo for BSC (p = 0.07; HR: 0.72)
• DCR 22.7% for D+T and 6.6% for BSC (p = 0.006)
Response to PD-1 Blockade in Microsatellite Stable Metastatic Colorectal Cancer Harboring a POLE Mutation

*J Natl Compr Canc Netw* 2017;15:142–147;
FDA Approves Merck’s Keytruda (pembrolizumab) for Previously Treated Patients with Recurrent Locally Advanced or Metastatic Gastric or Gastroesophageal Junction Cancer Whose Tumors Express PD-L1

KENILWORTH, N.J.—(BUSINESS WIRE) September 22, 2017

FDA Approves Keytruda (pembrolizumab) as First Cancer Treatment for any Solid Tumor with a Specific Genetic Feature

May 23, 2017 — The U.S. Food and Drug Administration today granted accelerated approval to a treatment for patients whose cancers have a specific genetic feature (biomarker). This is the first time the agency has approved a cancer treatment based on a common biomarker rather than the location in the body where the tumor originated.

Keytruda (pembrolizumab) is indicated for the treatment of adult and pediatric patients with unresectable or metastatic solid tumors that have been identified as having a biomarker referred to as microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR).

Opdivo (nivolumab) + Low-Dose Yervoy (ipilimumab) Combination Approved for Previously Treated MSI-H/dMMR Metastatic Colorectal Cancer

PRINCETON, N.J.— July 11, 2018 (BUSINESS WIRE)—

Bristol-Myers Squibb Receives FDA Approval for Opdivo (nivolumab) in MSI-H or dMMR Metastatic Colorectal Cancer That Has Progressed Following Treatment

PRINCETON, N.J.—(BUSINESS WIRE) August 1, 2017 —

Japan Ministry of Health, Labor and Welfare Approves Opdivo (nivolumab) for the Treatment of Patients with Unresectable Advanced or Recurrent Gastric Cancer Which Has Progressed After Chemotherapy

Opdivo is the first and only Immuno-Oncology treatment to demonstrate survival benefit in patients who underwent two or more prior treatments

Opdivo is the first Immuno-Oncology agent anywhere in the world to receive approval for unresectable advanced or recurrent gastric cancer based on a Phase 3 study

CATEGORY: CORPORATE/FINANCIAL NEWS
FRIDAY, SEPTEMBER 22, 2017 5:00 AM EDT
Biologic importance of Microsatellites

- **Microsatellites**, or short tandem repeats, are repetitive DNA sequences with a unit length ranging from one to six bases distributed along coding and noncoding regions of the genome.
- They are highly polymorphic among subjects but stable in each individual.
- The repetitive nature of these regions makes them particularly sensitive to mismatch errors.

![Diagram of repeated sequence of CAG (polyglutamine tract) with normal and abnormal replication and protein production](image-url)

Vilar & Gruber Nat Rev Clin Oncol 2010
DNA Mismatch Repair System

- DNAMismatch repair is a **highly conserved mechanism** involved in **restoring DNA integrity** after the occurrence of mismatching errors during DNA replication, recombination or iatrogenic damage.

- **Four genes** regulate the MMR mechanism: mutL homologue 1 (MLH1), mutS homologue 2 (MSH2), mutS homologue 6 (MSH6) and postmeiotic segregation increased 2 (PMS2).

- The four proteins codified by these genes form **heterodimers**:
  - MLH1/PMS2
  - MSH2/MSH6
Microsatellite Instability (MSI)

- Biallelic inactivation of one of the four genes coding for the MMR proteins implies a defective DNA mismatch repair system
- MSI is a hypermutable phenotype caused by the loss of DNA mismatch repair activity

This condition causes thousands of mutations and ultimately cancer

Vilar & Gruber Nat Rev Clin Oncol 2010
Terminology

- **MSI**
  - (microsatellite instable)
  - **dMMR**
    - (deficient mismatch repair)
  - Phenotype RER+ (Replication Error+)

- **MSS**
  - (microsatellite stable)
  - **pMMR**
    - (proficient mismatch repair)
  - Phenotype RER- (Replication Error-)
BRCA1/2 genomic alterations were strongly associated with gLOH-H in ovarian and breast cancer, but also (less strongly) in other cancer types.
BRCA and homologous recombination deficiency
Responses to platinum therapy

Liquid biopsy

• Challenges in cfDNA
  – The absolute levels are low (few nanograms per ml of plasma)
  – The circulating cell-free DNA (cfDNA) contains both tumor-derived DNA (ctDNA) and normal DNA from other dividing cells
  – The ctDNA is only a fraction (<0.1% to 50%) of the cfDNA
  – Levels are usually correlated with tumor burden (higher in advanced cancer)
  – Highly fragmented, short half live
Assessment of drug response and clonal evolution

- Liquid biopsies capture spatial and temporal heterogeneity underpinning resistance to anti-EGFR monoclonal antibodies in colorectal cancer.
Assessment of drug response and clonal evolution