Updates in Gastrointestinal (GI) Cancers
FLASCO Fall Session 2019
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Objectives

1. Design a treatment plan for microsatellite instability high and BRAF mutant subtypes of colorectal cancer (CRC) based on emerging data

2. Highlight the recent strides made in the management of metastatic hepatocellular carcinoma (HCC)

3. Outline the latest therapies approved in gastric and gastroesophageal junction (G/GEJ) cancers including immunotherapy and trifluridine/tipiracil

4. Analyze new approaches in the management of resectable pancreatic cancer and BRCA mutated pancreatic cancer
GI Cancers – An Urgent Need

- Consists of cancers of the esophagus, stomach, liver, pancreas, small intestine, colon, rectum and anus
- Overall #1 cancers in incidence and mortality
- Rising incidence in age <50 - up from 6% in 1990 to 11% in 2013
Approximately 15% of colorectal cancers (CRC) display high level of microsatellite instability (MSI-H).

Mutations affecting DNA mismatch repair genes: MLH1, MSH2, MSH6, PMS2

Distinct histologic features
- Mucin-rich, signet cell and medullary subtypes
- Active immune microenvironment as shown by an excess of tumor-infiltrating lymphocytes

MSI-H leads to thousands of improperly repaired mutant DNA

Production of mutant proteins that are targeted by the immune system

Suppression of immune response by PDL-1 on tumor cells

# Pembrolizumab in MSI-H

<table>
<thead>
<tr>
<th>Prior therapy</th>
<th>Le DT et al. (Keynote-016)</th>
<th>Le DT et al. (Keynote-164)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients</td>
<td>28</td>
<td>63</td>
</tr>
<tr>
<td>Dose</td>
<td>10 mg/kg q3 weeks up to 2 years</td>
<td>200 mg q3 weeks up to 2 years</td>
</tr>
<tr>
<td>ORR (%)</td>
<td>40</td>
<td>32</td>
</tr>
<tr>
<td>Duration of response</td>
<td>78% PFS at 5 months</td>
<td>41% PFS at 12 months</td>
</tr>
</tbody>
</table>

Pembrolizumab FDA approval in MSI-H mCRC: progression following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan


ORR = objective response rate
mCRC = metastatic colorectal cancer
# CheckMate-142 Study in MSI-H

<table>
<thead>
<tr>
<th>Prior therapy</th>
<th>Nivolumab (N) Cohort</th>
<th>Previously treated Ipilimumab (I) + Nivolumab Cohort</th>
<th>First line Ipilimumab + Nivolumab Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients</td>
<td>74</td>
<td>119</td>
<td>45</td>
</tr>
<tr>
<td>Dose</td>
<td>N 3 mg/kg q2w</td>
<td>N 3 mg/kg + I 1 mg/kg q3w x 4 doses, then N 3 mg/kg q2w</td>
<td>N 3 mg/kg q2w + I 1 mg/kg q6w</td>
</tr>
<tr>
<td>ORR (%)</td>
<td>31.1</td>
<td>55</td>
<td>60</td>
</tr>
<tr>
<td>Duration of response</td>
<td>PFS 50% at 12 months</td>
<td>PFS 71% at 12 months</td>
<td>83% at 12 months</td>
</tr>
<tr>
<td>Incidence of Grade 3 or 4 ADR (%)</td>
<td>20</td>
<td>33</td>
<td>16</td>
</tr>
</tbody>
</table>

Nivolumab FDA approval in MSI-H mCRC: progression following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan as a single agent or in combination with ipilimumab

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BRAF Mutations in CRC

• BRAF mutations occur in about 12% of CRC cases
  • More than 90% of these are V600E
  • Associated with poor differentiation, mucinous histology and microsatellite instability

• Poor outcomes - median OS <12 months

• BRAF inhibitor alone response - 2-5% ORR

# Clinical Data in BRAF Mutant CRC

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ORR (%)</th>
<th>PFS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vemurafenib (n=21)</td>
<td>5</td>
<td>2.1</td>
</tr>
<tr>
<td>Dabrafenib + trametinib (n=43)</td>
<td>12</td>
<td>3.5</td>
</tr>
<tr>
<td>Encorafenib + cetuximab (n=52)</td>
<td>19.2</td>
<td>3.72</td>
</tr>
<tr>
<td>Vemurafenib + cetuximab + irinotecan (n=54)</td>
<td>16</td>
<td>4.3</td>
</tr>
</tbody>
</table>

BEACON Trial – Study Design

• BRAF V600E mutant
• 1-2 prior therapies
• N = 665

Randomize

Arm A (triplet-therapy)
encorafenib + binimetinib +
cetuximab n=224

Arm B (doublet-therapy)
encorafenib + cetuximab
n=220

Arm C - FOLFIRI + cetuximab
or Irinotecan + cetuximab
n=221

Dosing:
Encorafenib 300 mg daily
Binimetinib 45 mg bid
Cetuximab 400 mg/m2 loading dose then, 250 mg/m2 weekly

BEACON Trial - Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Arm A (triplet), n=224</th>
<th>Arm B (doublet), n=221</th>
<th>Arm C (control), n=220</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, %</td>
<td>26</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td>Median OS, mo</td>
<td>9</td>
<td>8.4</td>
<td>5.4</td>
</tr>
<tr>
<td>≥Grade 3 ADR, %</td>
<td>58</td>
<td>50</td>
<td>61</td>
</tr>
</tbody>
</table>

Treatment related adverse events:
More GI side-effects with triplet-therapy vs. doublet-therapy.

Headache, musculoskeletal pain, arthralgia, and myalgia occurred more frequently in the doublet-therapy group than in the triplet-therapy.

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Hepatocellular Carcinoma – A Rising Trend

• New cases rising over the last decade on average 2% per year

HCC - New Cases and Deaths

NCCN 2017

Systemic Treatment Options

1. Sorafenib

NCCN 2019

Systemic Treatment Options

1. Sorafenib (first line and second line after lenvatinib)
2. Lenvatinib (first line)
3. Cabozantinib (second line)
4. Regorafenib (second line)
5. Ramucirumab (second line and AFP ≥400 ng/mL)
6. Pembrolizumab (second line)
7. Nivolumab (second line)

REFLECT Trial – Study Design

Global, phase 3, open-label, randomized, non-inferiority study design

- Unresectable HCC
- No prior therapy
- Child-Pugh Class A
- ECOG PS ≤ 1
- Adequate organ function
- N = 954

Primary Endpoint – OS
Secondary Endpoint – PFS, ORR

R

Levatinib 12 mg daily (weight ≥60 kg)
or Levatinib 8 mg (weight <60 kg)
n=478

Sorafenib 400 mg BID
n=476

**REFLECT Trial – Outcomes**

### Efficacy

<table>
<thead>
<tr>
<th></th>
<th>Lenvatinib</th>
<th>Sorafenib</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, mo</td>
<td>7.4</td>
<td>3.7</td>
<td>0.64 (0.55–0.75), p&lt;0.0001</td>
</tr>
<tr>
<td>Median OS, mo</td>
<td>13.6</td>
<td>12.3</td>
<td>0.92 (0.79–1.06)</td>
</tr>
</tbody>
</table>

### Grade 3 or 4 ADR

<table>
<thead>
<tr>
<th></th>
<th>Lenvatinib, %</th>
<th>Sorafenib, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>23</td>
<td>14</td>
</tr>
<tr>
<td>Palmar planter erythrodysaesthesia</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

Lenvatinib FDA approval: first-line treatment of unresectable hepatocellular carcinoma

TKI in Second Line HCC

**Regorafenib** (VEGF, PDGFR, RET etc.)

RESORCE study - regorafenib vs. placebo
- Child-Pugh Class A, previously tolerated at least sorafenib 400 mg daily
- Dose = 160 mg 3 weeks on 1 off

Results: Regorafenib improved median overall survival vs. placebo
- 10.6 months vs. 7.8 months, p<0.0001
- ADR: Hypertension, hand-foot syndrome and fatigue, increased LFT/bilirubin were common

**Cabozantinib** (CMET, PDGFR, VEGF, RET)

CELESTIAL study - cabozantinib vs. placebo
- Child-Pugh Class A, progressed on sorafenib
- Dose = 60 mg daily

Results: Cabozantinib improved median overall survival vs. placebo
- 10.2 months vs. 8.3 months, p=0.005
- ADR: hand-foot syndrome, hypertension, increased LFT, fatigue, diarrhea


TKI – Tyrosine kinase inhibitor, LFT – Liver function test
Nivolumab CheckMate-040 Study

Non-randomized, open label, phase 1/2, dose-escalation and expansion study

- Progression or intolerance to sorafenib
- Child-Pugh Score 7 or less (Class A or B7)
- ECOG PS 0-1
- Dose: 3 mg/kg q 2 weeks

Results

- n=48 in dose escalation cohort, n=214 in expansion cohort
- Objective RR 20% in dose escalation cohort
- Objective RR 15% in expansion cohort

FDA granted accelerated approval in September 2017, based on median duration of response of 16.2 months

Pembrolizumab Keynote-224 Study

Non-randomized, open label, phase 2 study design
  • Progression or intolerance to sorafenib
  • Child-Pugh Class A
  • ECOG PS 0-1
  • Dose: 200 mg every 3 weeks

Results
  • n=104
  • Objective RR 16.3%
  • Grade 3-4 ADR – 25%

At median follow up of 12.3 months, median duration of response was not reached

FDA granted accelerated approval in November 2018

HCC Immunotherapy Recent Updates

Phase 3 CheckMate-459 study

• Randomized study, comparing nivolumab vs. sorafenib in *first line* setting
• Failed to meet primary endpoint of improved OS

Phase 3 Keynote-240 study

• Randomized study, comparing pembrolizumab vs. placebo in *previously treated* HCC
• Failed to meet primary endpoint of improved PFS+OS
Ramucirumab – monoclonal antibody inhibiting activation of VEGFR2

**REACH trial** - Ramucirumab vs. placebo, 2nd line, n=565
- Did not improve primary endpoint of OS
- Subgroup analysis showed potentially improved outcomes in AFP ≥ 400 ng/mL

**REACH-2**, randomized, placebo-controlled, 2nd line, and baseline AFP ≥ 400 ng/mL, Child-Pugh class A
- Median OS improved with ramucirumab vs. placebo, 8.5 vs. 7.3 months, [HR] 0.710 [95% CI 0.531–0.949]; p=0.0199

May 2019 - FDA approved ramucirumab in 2nd line HCC and AFP ≥ 400 ng/mL


AFP – Alpha feto-protein
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Recent Approvals G/GEJ Tumors

- Feb 2019 - trifluridine/ tipiracil FDA approved for advanced or metastatic gastric/gastroesophageal junction (G/GEJ) adenocarcinoma, in third line setting

- May 2019 - Pembrolizumab FDA approved for advanced or metastatic esophageal squamous cell carcinoma (E-SCC) with CPS ≥ 10 in second line setting
  - 2017 – Pembrolizumab was previously approved for G/GEJ adenocarcinoma and CPS ≥ 1 in third line
TAGS Trial – Study Design

Randomized, double-blind, placebo-controlled study design

- G/GEJ Adenocarcinoma after at least 2 previous lines of therapy
- Adequate organ function
- N = 507
- Primary endpoint – overall survival

R 2:1

Trifluridine/Tipiracil (35 mg/m² BID on days 1–5 and 8–12) q28 days

Placebo

TAGS Trial - Results

<table>
<thead>
<tr>
<th></th>
<th>Trifluridine/Tipiracil</th>
<th>Placebo</th>
<th>Hazard Ratio [CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, mo</td>
<td>2</td>
<td>1.8</td>
<td>0.57 [0.47–0.70], p&lt;0.0001</td>
</tr>
<tr>
<td>Median OS, mo</td>
<td>5.7</td>
<td>3.6</td>
<td>0.69 [0.56–0.85], p=0.00029</td>
</tr>
</tbody>
</table>

Most common grade 3-4 ADR with trifluridine/tipiracil
- Anemia (19%), neutropenia (25%), fatigue (7%) and decreased appetite (8%)
Pembrolizumab for Esophageal SCC

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>KN-181</th>
<th>KN-180</th>
</tr>
</thead>
<tbody>
<tr>
<td>E-SCC, CPS ≥ 10</td>
<td>E-SCC, CPS ≥ 10</td>
<td></td>
</tr>
<tr>
<td>Prior therapy</td>
<td>Progression after 1st line therapy</td>
<td>Progression after 2 or more lines of therapy</td>
</tr>
<tr>
<td>Number of patients</td>
<td>85</td>
<td>35</td>
</tr>
<tr>
<td>ORR, %</td>
<td>22</td>
<td>20</td>
</tr>
<tr>
<td>Survival</td>
<td>Median OS 10.3 months</td>
<td>71% of responders alive at 6 months</td>
</tr>
</tbody>
</table>

May 2019 - FDA approved in second-line setting for esophageal SCC (E-SCC) and CPS ≥ 10

Nivolumab E-SCC – ATTRACTION-3 Trial

Phase 3, randomized, open label in patients with advanced E-SCC, progressed on one line of therapy

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab</th>
<th>Investigator Choice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>210</td>
<td>209</td>
</tr>
<tr>
<td>ORR, %</td>
<td>19</td>
<td>22</td>
</tr>
<tr>
<td>Survival*</td>
<td>10.9</td>
<td>8.4</td>
</tr>
</tbody>
</table>

*P=0.0019

96% of patient population was Asian → Global generalizability?


Investigator choice chemotherapy: paclitaxel, irinotecan or docetaxel
Keynote-062 - First Line G/GEJ

Keynote-062 - randomized, phase 3 study, **first-line** G/GEJ adenocarcinoma tumors:

- 5-FU + platinum based chemo (C) vs.
- Pembrolizumab (P) monotherapy vs.
- P+C

P+C did not meet primary endpoint for superiority vs. C

OS with P was non-inferior compared to C (10.6 months vs. 11.1 months)

Subgroups with CPS ≥ 10 or MSI-H had a greater response from immunotherapy

Tabernero et al. J Clin Oncol 37, 2019 (suppl; abstr LBA4007)
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Pancreatic Cancer

- Cure rate: 8%

- Moved from fourth leading cause of cancer-related death to third in 2016
  - Expected to become 2nd leading cause within the next decade

- Despite “curative” surgery less than 4% patients will survive 10 years or more
No significant advance in adjuvant treatment of pancreatic cancer in 30 years
• Best median OS has been around 28 months
• Gemcitabine +/- capecitabine was historical standard of care

This changed with the results from a phase III study comparing mFOLFIRINOX vs. gemcitabine

mFOLFIRINOX regimen:
• Oxaliplatin 85 mg/m2
• Leucovorin 400 mg/m2
• Irinotecan 150 mg/m2 (reduced from 185 mg/m2 after interim safety analysis)
• 5-FU 2400 mg/m2 CIVI over 46 hours
• No 5-FU bolus

Multicenter, randomized, open-label, phase 3 trial conducted in France and Canada

- Pancreatic adenocarcinoma s/p R0 or R1 surgery
- Allowed up to 12 weeks of recovery from surgery
- Age 18-79; ECOG PS 0-1
- Randomized, open-label, multicenter study design
- Primary endpoint: disease free survival (DFS)

- Gemcitabine 1000 mg/m2 on days 1, 8, 15 every 28 days for 24 weeks
  - n=246

- mFOLFINOX regimen every 14 days for 24 weeks
  - n=247

PRODIGE 24/CCTG PA.6 – Results

<table>
<thead>
<tr>
<th></th>
<th>mFOLFIRINOX</th>
<th>Gemcitabine</th>
<th>Hazard Ratio and CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median DFS, mo</td>
<td>21.6</td>
<td>12.8</td>
<td>0.58 (0.46–0.73), p&lt;0.001</td>
</tr>
<tr>
<td>Median OS, mo</td>
<td>54.4</td>
<td>35</td>
<td>0.64 (0.48–0.86), p=0.003</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade 3 or 4 ADR</th>
<th>mFOLFIRINOX, %</th>
<th>Gemcitabine, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea/Vomiting</td>
<td>10.6</td>
<td>2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>11</td>
<td>4.6</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>18.6</td>
<td>3.7</td>
</tr>
<tr>
<td>Paresthesia/Sensory neuropathy</td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>1.3</td>
<td>4.5</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>28.4</td>
<td>26</td>
</tr>
</tbody>
</table>

mFOLFIRINOX – is now the new standard of care in adjuvant pancreatic cancer after R0 or R1 surgery

Global, randomized, double-blind, placebo-controlled, phase 3 trial

- Metastatic Pancreatic Cancer
- Germline BRCA mutation
- Responder to platinum based chemo after at least 16 weeks of treatment
- Primary endpoint – Progression free survival
- N = 154

R 3:2

Olaparib 300 mg bid, n=92

Placebo, n=62

## POLO Study Results

<table>
<thead>
<tr>
<th></th>
<th>Olaparib</th>
<th>Placebo</th>
<th>Hazard Ratio [CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, mo</td>
<td>7.4</td>
<td>3.8</td>
<td>0.53 [0.35–0.82], p=0.004</td>
</tr>
<tr>
<td>Median OS, mo (interim analysis)</td>
<td>18.9</td>
<td>18.1</td>
<td>0.91 [0.56–1.46], p=0.68</td>
</tr>
</tbody>
</table>

- Most common grade 3-4 ADR: anemia (11%), fatigue (5%), decreased appetite (3%)
- No difference in health-related quality of life between 2 groups

1. Pembrolizumab, nivolumab and combination of nivolumab + ipilimumab are approved in MSI-H mCRC. Benefit appears to be of the highest magnitude with combination regimen.

2. BRAF mutated mCRC carries a poor prognosis. Recent studies indicate a combination of BRAF inhibitor, MEK inhibitor AND EGFR inhibitor improves ORR and OS vs. chemotherapy alone.

3. Several new options, including TKI, anti-VEGFR monoclonal antibody and immunotherapy, are now available in HCC compared to just a few years ago.

4. Trifluridine/tipiracil was recently approved in G/GEJ cancers in the third line setting. Pembrolizumab is now a second-line option in patients with E-SCC and CPS≥ 10.

5. mFOLFIRINOX is the new standard of care in adjuvant treatment of pancreatic cancer.
Questions?

Acknowledgements:

- FLASCO & Program Committee
- Moffitt GI Med-Onc and Pharmacy Team
- Our patients