Clarion Perspectives from the

2019 World Congress on GI Cancers

July 3–6, 2019 • Barcelona, Spain

We saw exciting advances in molecular targeted therapy across a range of GI cancer types, likely to drive future expansion of biomarker testing

Targeted Therapy: A Shining BEACON in Colorectal Cancer (CRC)

- **BRAFi ± MEKi + EGFRi combination emerges as a new, chemo-free standard of care for BRAF-mutant CRC**
  - In the phase 3 BEACON trial for second-line (2L), BRAF V600E-mutant mCRC, both the **encorafenib + binimetinib (Braftovi + Mektovi) [Array] + cetuximab (Erbitux) [Eli Lilly]** triplet and the **encorafenib + cetuximab** doublet were clearly superior to chemo (FOLFIRI or irinotecan) + cetuximab: mOS = 9.0 mo for the triplet, 8.4 mo for the doublet, vs 5.4 for the chemo-based control[1]
  - The encorafenib + binimetinib + cetuximab triplet is now in a phase 2 trial (ANCHOR) in the 1L setting[2]
- **Other targeted therapy combinations are expected to emerge**
  - **Anti-TA-MUC1** (tumor-associated epitope of mucin-1 antibody) **gatipotuzumab [Glycotope]** combined with **anti-EGFR tomuzotuximab [Glycotope]** in the phase 1 dose-finding GATTO trial produced responses in 2 of 4 pretreated, KRAS wild-type mCRC patients—an impressive signal in the absence of chemotherapy[3]
  - **PARP inhibitors** warrant study, since as many as 32% of CRC patients may have mutations in DNA damage repair pathways associated with PARP inhibitor (and platinum chemotherapy) efficacy in other tumor types[4]
  - Without biomarker selection, the multi-TKI **merestinib** + **anti-VEGFR ramucirumab (Cyramza) [Eli Lilly]** had ORR = 0% (n=23) in a phase 1 study, though mOS was a respectable 8.9 months in heavily pretreated mCRC[5]

1) World GI 2019 #LBA-006; 2) #P-400; 3) #SO-010; 4) PD-022; 5) #SO-008

Success Targeting Rare Segments of Pancreatic Cancer

- **PARP inhibition for *BRCA*-mutant pancreatic ductal adenocarcinoma (PDAC) continues to shine**
  - As previously reported at ASCO 2019, the POLO trial of PARP inhibitor **olaparib (Lynparza) [AstraZeneca]** as 1L maintenance therapy reported near doubling of mPFS (7.4 vs 3.8 mo for placebo) and >6-fold increase in mDoR (24.9 vs 3.7 mo) for the 4–7% of PDAC patients who have germline *BRCA* mutation[1,2]
  - At World GI, disease control rates for POLO patients were reported, and were also impressive: 74% as best response and 53% at 16 weeks with olaparib, versus 64% and 37% with placebo[2]
- **EGFR/HER2 inhibition may address PDAC harboring NRG1 fusions**
  - Neuregulin is a ligand of the ErbB family of receptors which includes EGFR, HER2, and HER3. Genomic analysis shows that NRG1 fusions are enriched in KRAS wild-type PDAC, an under-recognized subgroup[3]
  - Case reports show that NRG1-fusion PDAC patients may respond to EGFRi + anti-HER2 therapy **erlotinib (Tarceva) + pertuzumab (Perjeta) [Roche]** or single-agent ErbB family inhibitor **afatinib (Gilotrif) [BI]**[3,4]
- **Non-biomarker-based approaches continue to flounder**
  - Therapies added to standard chemo without biomarker selection usually fail. One of the latest examples: phase 3 RESOLVE study of BTK inhibitor **ibrutinib (Imbruvica) [AbbVie/JNJ]** added to gemcitabine + nab-paclitaxel for 1L mPDAC failed to improve efficacy versus chemo alone[5]

1) ASCO 2019 #LBA4; 2) World GI 2019 #LBA-001; 3) O'Reilly, "Genetics and Molecular Alterations in Pancreatic Cancer"; 4) #P-291; 5) #O-002

Success Targeting Oncogenic Fusions Regardless of Histology

- **Targeting NTRK fusions has strong efficacy in GI cancers**
  - **Entrectinib [Roche/Ignyta]** has ORR of 57% across solid tumors harboring an NTRK fusion[1]; it is now under FDA review for a histology-agnostic indication similar to **larotrectinib (Vitrakvi) [Bayer/Loxo**][2]. For the GI cancers in entrectinib's dataset, the ORR was 50% (4/8) consistent with the broader sample[3]
- **Targeting FGFR fusions has moderate efficacy in GI cancers**
  - **Debio 1347 [Debiopharm]** induced responses in 3/9 GI cancers (CRC and biliary) with FGFR fusion in its phase 1 trial; a phase 2 trial (FUZE) is ongoing[4]
- **Unlike fusions, targeting FLT3 amplification alone is insufficient**
  - In contrast, **sunitinib (Sutent) [Pfizer]** had 0% ORR in FLT3-amplified mCRC. Foundation Medicine explained this, showing that FLT3 amplification (unlike HER2) lacks the hallmarks of an oncogenic driver[5]

1) Roche press release Feb 19, 2019; 2) FDA; 3) World GI 2019 #O-024; 4) #SO-003; 5) #O-009

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Immunotherapy Continues to Glimmer with Promise

Although immuno-oncology progress remains slow in GI cancers, we see promising results continue to emerge across multiple tumor types

- **Gastric/esophageal: Anti-PD1 moves earlier, but better biomarkers and/or combinations are needed**
  - **Pembrolizumab (Keytruda)[Merck]** is already approved for 3L+ advanced gastric cancer[1]; as reported at ASCO[2,3], pembro also completed phase 3 studies in 1L gastric cancer (Keynote-062)[4,] and 2L esophageal cancer (Keynote-181)[5.] Results were mixed. For patients with high PD-L1 (CPS ≥10), pembro alone has better mOS than chemo (1L gastric: 17.4 vs 10.8 mo; 2L esophageal: 9.3 vs 6.7 mo) but *worse* mPFS. Pembro + chemo only modestly improves efficacy vs chemo for CPS ≥1, 1L gastric. Although sufficient for pembro to become a SoC option, these results show that only a subset of PD-L1+ patients truly benefit
  - Combinations with anti-VEGFR **ramucirumab (Cyramza) [Eli Lilly]** hold some promise. In a phase 1b study, **pembro + ramucirumab** showed efficacy in 1L gastric cancer: ORR 25%, mPFS 5.6 mo, mOS 14.6 mo; the numbers were even higher for PD-L1+ patients[6]. In a phase 1/2 study, **nivolumab (Opdivo) [BMS] + ramucirumab + paclitaxel** showed efficacy in 2L gastric cancer: ORR 37%, mPFS 5.1 mo (n=43)[7]
  - However, in the phase 1b REGONIVO trial, **nivo + regorafenib (Stivarga) [Bayer]**, a TKI, was even more impressive, and in 3L or later: ORR 44%, mPFS 5.8 mo (n=25); even better for PD-L1+ or TMB high patients[8]
- **Hepatocellular carcinoma (HCC): Anti-PD1 remains a 2L option; may break into the (neo)adjuvant setting**
  - **Pembro** obtained accelerated approval for 2L HCC based on a single-arm trial[1]. The confirmatory Keynote-240 trial missed its primary endpoints, but still showed better efficacy for pembro vs placebo: e.g., mOS = 13.9 vs 10.6 mo with HR = 0.781, but the target HR was 0.75[9,10]
  - **Nivo ± ipilimumab (Yervoy) [BMS]** shows promise as neoadjuvant + adjuvant therapy, producing a pCR of 29%[11.] A phase 3 adjuvant trial of **durvalumab (Imfinzi) [AZ] ± bevacizumab (Avastin) [Roche]** is ongoing[12]
- **Colorectal cancer (CRC): A variety of I-O approaches show promise in early exploratory trials**
  - **Nivo + regorafenib** has compelling efficacy not only in gastric cancer but also in 3L+ CRC (ORR 36%, mPFS 6.3 mo); however, unlike gastric, PD-L1 and high TMB do not seem to predict higher PFS in CRC (phase 1b)[8]
  - **Nivo + ipi + radiation therapy (RT)** produced an objective response rate of 15–18% in lesions outside of the RT field in both 3L+ CRC and PDAC, suggestive of a weak abscopal effect[13]
  - **Neoadjuvant CRT + nivo** produced a pCR of 30% in microsatellite stable rectal cancer (phase 1b/2)[14]
  - **NKG2D-targeted CAR-T** cell therapies show modest efficacy—1/9 patients responded to autologous CAR-T, and 1/6 to allogenic CAR-T. The proof of principle is exciting, especially for allogeneic CAR-T (phase 1)[15]

1) FDA; 2) ASCO 2019 #LBA4007; 3) #4010; 4) World GI 2019 #LBA-002; 5) #O-012; 6) #SO-002: 7) #SO-001; 8) #SO-007; 9) ASCO 2019 #4004; 10) World GI 2019 #O-027; 11) #PD-009; 12) #P-217; 13) #O-008; 14) #O-010; 15) #SO-009

Cytotoxic Chemotherapy Continues to Be Refined

Despite decades of use, there is still more to learn about optimizing our use of chemo

- **1L chemo standards of care continue to shift**
  - In 1L CRC, the evidence favoring **FOLFOXIRI** (5-FU/LV + oxaliplatin + irinotecan) over FOLFOX or FOLFIRI continues to grow, including combinations of FOLFOXIRI + different biologic agents[1,2,3,4]
  - In 1L PDAC, **nal-irinotecan (Onivyde) [Ipsen] + 5-FU/LV + oxaliplatin** may be competitive with FOLFIRINOX[5]
  - In 1L gastric cancer, **TAS-118 [Taiho]**, a combination of leucovorin (LV) + S-1—**tegafur/gimeracil/oteracil (Teysuno) [Taiho]**, a 5-FU prodrug product—is slightly more efficacious than S-1, in platinum combinations[6]
- **Repeat treatment may be better than alternating backbones in CRC**
  - Repeating FOLFIRINOX or FOLFIRI was more efficacious than 1L/2L switching between FOLFOX/FOLFIRI[1,7].
  - Rechallenge with a prior chemo regimen in the salvage setting is superior to regorafenib or TAS-102[8]
- **Are we overtreating or undertreating early-stage CRC?**
  - The Oncotype DX 12-gene recurrence score leads to a recommendation of more treatment for 8% and less treatment for 32% of stage II/III CRCs[9]. Immunoscore testing reveals different risk levels even in stage I[10]

1) World GI 2019 #LBA-007; 2) #O-013; 3) #P-099; 4) #PD-030; 5) #SO-005; 6) #LBA-003; 7) #O-015; 8) #P-139; 9)#O-17; 10) #O-023

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